EXHIBIT A

IN THE UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF FLORIDA
TAMPA DIVISION

AZURITY PHARMACEUTICALS, INC.,	)	
Plaintiff,	)	
v.	)	Case No. 8:21-cv-2515
CORERX, INC.,	)	**JURY TRIAL DEMANDED**
Defendant.	)	

COMPLAINT FOR PATENT INFRINGEMENT

For its Complaint against Defendant CoreRx, Inc. ("CoreRx" or "Defendant"), Plaintiff Azurity Pharmaceuticals, Inc. ("Azurity" or "Plaintiff"), by and through its attorneys, alleges as follows:

THE NATURE OF THE ACTION

1. This is an action for patent infringement of United States Patent Nos. 11,040,023 (the "'023 patent") and 11,141,405 (the "'405 patent") (collectively the "Patents-in-Suit") and damages under the patent laws of the United States, Title 35, United States Code, that arises out of CoreRx's manufacture, use, sale, importation, and/or offer to sell and/or inducement of or contributing to others to do the foregoing within the United States of the product that is the subject of Bionpharma Inc.'s ("Bionpharma") ANDA No. 212408 ("CoreRx Formulation") prior to the expiration of the Patents-in-Suit. Azurity seeks all available relief under the patent laws of the

United States, 35 U.S.C. § 100 *et. seq.*, and any other applicable laws for CoreRx's infringement of the Patents-in-Suit.

THE PARTIES

2. Azurity is a corporation organized and existing under the laws of the State of Delaware, with a principal place of business at 8 Cabot Road, Suite 2000, Woburn, MA 01801.

3. On information and belief, CoreRx is a corporation organized and existing under the laws of the State of Florida, with its principal place of business at 14205 Myerlake Cir., Clearwater, FL 33760. On information and belief, CoreRx is in the business of, among other things, developing, manufacturing, and selling generic copies of branded pharmaceutical products for the U.S. market.

JURISDICTION AND VENUE

4. This action arises under the patent laws of the United States of America, 35 U.S.C. § 1, *et seq.*, and from CoreRx's manufacture, use, sale, importation, and/or offer to sell and/or inducement of or contributing to others to do the foregoing within the United States of the CoreRx Formulation before the expiration of the Patents-in-Suit.

5. This Court has subject matter jurisdiction over the action under 28 U.S.C. §§ 1331, 1338(a) (patent infringement). Relief is sought under 35 U.S.C. §§ 271(a)-(c).

6. This Court has personal jurisdiction over CoreRx because, among other things, on information and belief, CoreRx is a corporation formed under the laws of the State of Florida that maintains a principal place of business in Florida.

7. Venue is proper in this Court under 28 U.S.C. §§ 1391(c) and 1400(b).

AZURITY'S EPANED® PRODUCT

8. Azurity holds approved NDA No. 208686 for a ready-to-use oral solution of enalapril maleate, which is prescribed and sold under the trade name Epaned®.

9. Azurity's Epaned® product is the first FDA approved ace inhibitor treatment that is a ready-to-use oral solution for hypertension in children under six years of age. Epaned® is also indicated to treat hypertension in adults, heart failure, and asymptomatic left ventricular dysfunction.

PATENTS-IN-SUIT

10. The '023 patent, entitled "Enalapril Formulations," issued on June 22, 2021. A true and correct copy of the '023 patent is attached to this Complaint as Exhibit A.

11. The '023 patent was duly and legally issued to Azurity as the assignee and Azurity owns all rights, title, and interest in the '023 patent.

12. Pursuant to 21 U.S.C. § 355, the '023 patent is listed in the Approved Drug Products with Therapeutic Equivalence Evaluations ("the Orange Book") in connection with Azurity's Epaned® product.

13. The '023 patent describes stable, oral liquid formulations of enalapril.

14. The '023 patent expires on March 25, 2036.

15. The ’405 patent, entitled “Enalapril Formulations,” issued on October 12, 2021. A true and correct copy of the ’405 patent is attached to this Complaint as Exhibit B.

16. The ’405 patent was duly and legally issued to Azurity as the assignee and Azurity owns all rights, title, and interest in the ’405 patent.

17. Pursuant to 21 U.S.C. § 355, the ’405 patent is listed in the Orange Book in connection with Azurity’s Epaned® product.

18. The ’405 patent describes stable, oral liquid formulations of enalapril.

19. The ’405 patent expires on March 25, 2036.

INFRINGEMENT BY CORERX

20. On information and belief, CoreRx developed, manufactures, and sells the CoreRx Formulation.

21. On June 22, 2021, Azurity brought an action against Bionpharma alleging that the filing of ANDA No. 212408 was an act of infringement of the ’023 patent because the CoreRx Formulation is covered by one or more claims in the ’023 patent. That case is captioned *Azurity Pharmaceuticals, Inc. v. Bionpharma Inc.*, C.A. No. 21-1286-LPS (D. Del.) (“the ’023 Bionpharma Action”).

22. During prior litigation regarding ANDA No. 212408, CoreRx was represented by the same counsel that represented Bionpharma. *See Silvergate Pharmaceuticals, Inc. v. Bionpharma Inc.*, C.A. No. 18-1962-LPS, D.I. 56 (D. Del. Mar. 13, 2020) & C.A. No. 19-1067-LPS, D.I. 68 (D. Del. Mar. 13, 2020).

23. On information and belief, CoreRx is aware of the '023 Bionpharma Action.

24. On information and belief, CoreRx is aware that Azurity, in the '023 Bionpharma Action, filed a motion for preliminary injunction ("Azurity's PI Motion") seeking to enjoin the sale of the CoreRx Formulation.

25. On information and belief, CoreRx is aware that Bionpharma, in response to Azurity's PI Motion, does not deny that the CoreRx Formulation infringes several claims of the '023 patent.

26. On October 15, 2021, Azurity brought an action against Bionpharma for infringement of the '405 patent. That case is captioned *Azurity Pharmaceuticals, Inc. v. Bionpharma Inc.*, C.A. No. 21-1455-LPS (D. Del.) ("the '405 Bionpharma Action").

27. On information and belief, CoreRx is aware of the '405 Bionpharma Action.

28. The Patents-in-Suit expire on March 25, 2036.

29. On information and belief, on August 10, 2021, several weeks after the '023 patent legally issued from the United States Patent and Trademark Office and Azurity brought suit for infringement of the '023 patent against Bionpharma, ANDA No. 212408 was approved by FDA. Thereafter, in blatant disregard for Azurity's patent rights, Bionpharma began offering for sale and selling the CoreRx Formulation which, on information and belief, was manufactured by CoreRx.

30. On information and belief, CoreRx has and continues to engage in the commercial manufacture and sale of the CoreRx Formulation before the expiration of the Patents-in-Suit with the knowledge and intent to infringe the Patents-in-Suit.

31. On information and belief, the CoreRx Formulation infringes at least one claim of the Patents-in-Suit, including at least claim 1 of the '023 patent and claim 1 of the '405 patent, under at least one of 35 U.S.C. § 271(a), (b), and/or (c).

32. On information and belief, under 35 U.S.C. § 271(a)-(c), CoreRx has knowingly, willfully, repeatedly, and continually infringed at least one claim of the Patents-in-Suit, including at least claim 1 of the '023 patent and claim 1 of the '405 patent, by manufacturing, using, offering for sale, selling, and/or importing the CoreRx Formulation, and/or inducement of or contributing to others to do the foregoing in the United States before the expiration date of the Patents-in-Suit.

CLAIMS FOR RELIEF

Count I

(Infringement of the '023 Patent Under 35 U.S.C. § 271(a)-(c))

33. Azurity realleges and incorporates paragraphs 1 through 32 as if fully set forth herein.

34. On information and belief, the CoreRx Formulation has received final approval from FDA.

35. On information and belief, CoreRx has engaged in and/or induced and continues to induce another, including Bionpharma, to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of the CoreRx Formulation.

CoreRx's acts of infringement have irreparably injured and damaged and continue to irreparably injure and damage Azurity.

36. The commercial manufacture, use, offer for sale, sale, and/or importation of the CoreRx Formulation is an act of direct infringement of one or more claims of the '023 patent under 35 U.S.C. § 271(a), including at least claim 1 of the '023 patent.

37. On information and belief, CoreRx is inducing infringement of one or more claims of the '023 patent under 35 U.S.C. § 271(b) by inducing the making, using, offering to sell, selling, and/or importation of the CoreRx Formulation in the United States. On information and belief, CoreRx is intentionally encouraging acts of direct infringement with knowledge of the '023 patent and knowledge that its acts are encouraging infringement.

38. On information and belief, CoreRx is contributorily infringing one or more claims of the '023 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing the CoreRx Formulation in the United States. On information and belief, CoreRx, through offering to sell or selling the CoreRx Formulation, has offered to sell or sold, and continues to do so, within the United States or import into the United States a component of a composition or material for use in practicing one or more claims of the '023 patent. On information and belief, CoreRx conducts and has conducted such activities knowing such component of a composition or material to be especially adapted for a use that infringes one or more

claims of the '023 patent and is not a staple article or commodity of commerce suitable for substantial noninfringing use.

39. The foregoing actions by CoreRx constitute infringement of the '023 patent.

40. CoreRx is committing those acts of infringement without license or authorization.

41. CoreRx is committing those acts of infringement despite its knowledge of both the '023 patent and the '023 Bionpharma Action.

42. Azurity is entitled to a judgement that the commercial manufacture, use, offer for sale, sale, and/or importation of the CoreRx Formulation infringes the '023 patent.

43. Azurity has suffered and will continue to suffer financial harm as a result of CoreRx's infringing activities.

44. The commercial manufacture, use, offer for sale, sale, and/or importation of the CoreRx Formulation in violation of Azurity's patent rights has caused and is continuing to cause substantial and irreparable harm to Azurity for which damages are inadequate.

45. Azurity is entitled to monetary damages but, because the infringement by CoreRx of the '023 patent will continue to cause Azurity irreparable injury and damage for which there is no adequate remedy at law unless and until CoreRx is enjoined from infringing the '023 patent, Azurity has no complete, adequate remedy at law and, therefore, is entitled to injunctive relief.

Count II

(Infringement of the '405 Patent Under 35 U.S.C. § 271(a)-(c))

46. Azurity realleges and incorporates paragraphs 1 through 32 as if fully set forth herein.

47. On information and belief, the CoreRx Formulation has received final approval from FDA.

48. On information and belief, CoreRx has engaged in and/or induced and continues to induce another, including Bionpharma, to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of the CoreRx Formulation. CoreRx's acts of infringement have irreparably injured and damaged and continue to irreparably injure and damage Azurity.

49. The commercial manufacture, use, offer for sale, sale, and/or importation of the CoreRx Formulation is an act of direct infringement of one or more claims of the '405 patent under 35 U.S.C. § 271(a), including at least claim 1 of the '405 patent.

50. On information and belief, CoreRx is inducing infringement of one or more claims of the '405 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing the CoreRx Formulation in the United States. On information and belief, CoreRx is intentionally encouraging acts of direct infringement with knowledge of the '405 patent and knowledge that its acts are encouraging infringement.

51. On information and belief, CoreRx is contributorily infringing one or more claims of the '405 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing the CoreRx Formulation in the United States. On information and belief, CoreRx, through offering to sell or selling the CoreRx Formulation, has offered to sell or sold, and continues to do so, within the United States or import into the United States a component of a composition or material for use in practicing one or more claims of the '405 patent. On information and belief, CoreRx conducts and has conducted such activities knowing such component of a composition or material to be especially adapted for a use that infringes one or more claims of the '405 patent and is not a staple article or commodity of commerce suitable for substantial noninfringing use.

52. The foregoing actions by CoreRx constitute infringement of the '405 patent.

53. CoreRx is committing those acts of infringement without license or authorization.

54. CoreRx is committing those acts of infringement despite its knowledge of both the '405 patent and the '405 Bionpharma Action Azurity is entitled to a judgement that the commercial manufacture, use, offer for sale, sale, and/or importation of the CoreRx Formulation infringes the '405 patent.

55. Azurity has suffered and will continue to suffer financial harm as a result of CoreRx's infringing activities.

56. The commercial manufacture, use, offer for sale, sale, and/or importation of the CoreRx Formulation in violation of Azurity's patent rights has caused and is continuing to cause substantial and irreparable harm to Azurity for which damages are inadequate.

57. Azurity is entitled to monetary damages but, because the infringement by CoreRx of the '405 patent will continue to cause Azurity irreparable injury and damage for which there is no adequate remedy at law unless and until CoreRx is enjoined from infringing the '405 patent, Azurity has no complete, adequate remedy at law and, therefore, is entitled to injunctive relief.

PRAYER FOR RELIEF

Azurity respectfully requests the following relief:

a) A finding that the Patents-in-Suit are valid and enforceable;

b) A judgment that CoreRx's making, using, offering to sell, or selling in the United States, or importing into the United States of the CoreRx Formulation directly infringes one or more claims of the Patents-in-Suit;

c) A judgment that CoreRx has induced infringement of the Patents-in-Suit by encouraging others to use, sell, offer for sale, and/or import the CoreRx Formulation in the United States before the expiration of the Patents-in-Suit;

d) A judgment that CoreRx has contributorily infringed the Patents-in-Suit by offering to sell or selling the CoreRx Formulation in the United States before the expiration of the Patents-in-Suit, knowing the same is especially adapted for a use that

directly infringes the Patents-in-Suit and that there is no substantial non-infringing use for the CoreRx Formulation;

e) A judgment that CoreRx's infringement was and is willful;

f) A finding that Azurity be awarded all damages adequate to compensate it for CoreRx's past infringement and any continuing or future infringement of the Patents-in-Suit in addition to interest and costs;

g) A permanent injunction enjoining CoreRx, and its subsidiaries, parents, officers, agents, servants, employees, licensees, representatives, and attorneys, and all other persons acting or attempting to act in active concert or participation with it or acting on its behalf, from engaging in the commercial manufacture use, offer to sell, or importation into the United States, of any drug product covered by the Patents-in-Suit, including the CoreRx Formulation, until the expiration of the Patents-in-Suit;

h) A finding that CoreRx's infringement is willful and that the monetary damages awarded to Azurity be trebled and include pre- and post-judgment interest, costs, and disbursements pursuant to 35 U.S.C. § 284;

i) A finding that this action for infringement is an exceptional case under 35 U.S.C. § 285, and that CoreRx is responsible for payment of Azurity's attorneys' fees and costs;

j) An award of any such other and further relief as the Court may deem just and proper.

DEMAND FOR JURY TRIAL

Plaintiff Azurity hereby demands a trial by jury on all issues so triable

October 26, 2021

/Woodrow H. Pollack/

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Attorneys for Plaintiff

Exhibit A

US011040023B2

(12) **United States Patent**
Mosher et al.

(10) **Patent No.: US 11,040,023 B2**
(45) **Date of Patent: *Jun. 22, 2021**

(54) **ENALAPRIL FORMULATIONS**

(71) Applicant: **Silvergate Pharmaceuticals, Inc.**, Greenwood Village, CO (US)

(72) Inventors: **Gerold L. Mosher**, Kansas City, MO (US); **David W. Miles**, Kansas City, MO (US)

(73) Assignee: **SILVERGATE PHARMACEUTICALS, INC.**, Greenwood Village, CO (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **17/150,587**

(22) Filed: **Jan. 15, 2021**

(65) **Prior Publication Data**

US 2021/0137882 A1 May 13, 2021

Related U.S. Application Data

(63) Continuation of application No. 16/991,575, filed on Aug. 12, 2020, now Pat. No. 10,918,621, which is a continuation of application No. 16/883,553, filed on May 26, 2020, now Pat. No. 10,799,476, which is a continuation of application No. 16/242,898, filed on Jan. 8, 2019, now Pat. No. 10,772,868, which is a

(Continued)

(51) **Int. Cl.**

A61K 31/401	(2006.01)
A61K 9/00	(2006.01)
A61K 47/26	(2006.01)
A61K 47/12	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 31/401*** (2013.01); ***A61K 9/0053*** (2013.01); ***A61K 9/0095*** (2013.01); ***A61K 47/12*** (2013.01); ***A61K 47/26*** (2013.01)

(58) **Field of Classification Search**

CPC A61K 31/401; A61K 47/12; A61K 47/26; A61K 9/0053; A61K 9/0095

See application file for complete search history.

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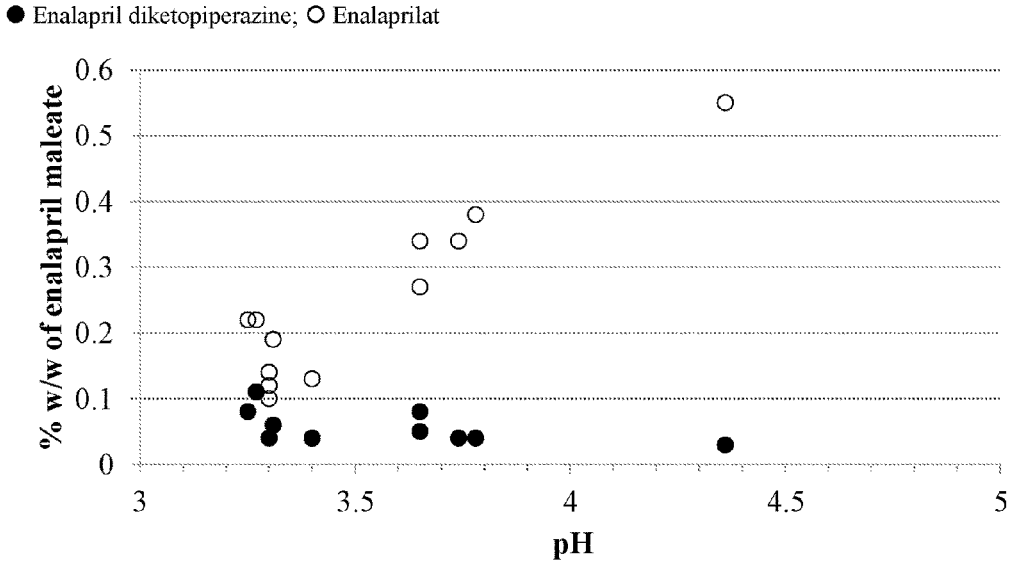
Primary Examiner — Savitha M Rao

(74) *Attorney, Agent, or Firm* — Wilson Sonsini Goodrich & Rosati

(57) **ABSTRACT**

Provided herein are stable enalapril oral liquid formulations. Also provided herein are methods of using enalapril oral liquid formulations for the treatment of certain diseases including hypertension, heart failure and asymptomatic left ventricular dysfunction.

20 Claims, 2 Drawing Sheets



Related U.S. Application Data

continuation of application No. 16/177,159, filed on Oct. 31, 2018, now Pat. No. 10,786,482, which is a continuation of application No. 16/003,994, filed on Jun. 8, 2018, now Pat. No. 10,154,987, which is a continuation of application No. 15/802,341, filed on Nov. 2, 2017, now Pat. No. 10,039,745, which is a continuation of application No. 15/613,622, filed on Jun. 5, 2017, now Pat. No. 9,808,442, which is a continuation of application No. 15/081,603, filed on Mar. 25, 2016, now Pat. No. 9,669,008.

(60) Provisional application No. 62/310,198, filed on Mar. 18, 2016.

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U.S. Appl. No. 15/613,622 Office Action dated Aug. 11, 2017.
U.S. Appl. No. 15/850,732 Office Action dated Mar. 1, 2018.
U.S. Appl. No. 16/003,994 Office Action dated Sep. 20, 2018.
U.S. Appl. No. 16/177,159 Advisory Action dated Sep. 16, 2019.
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FIG. 1

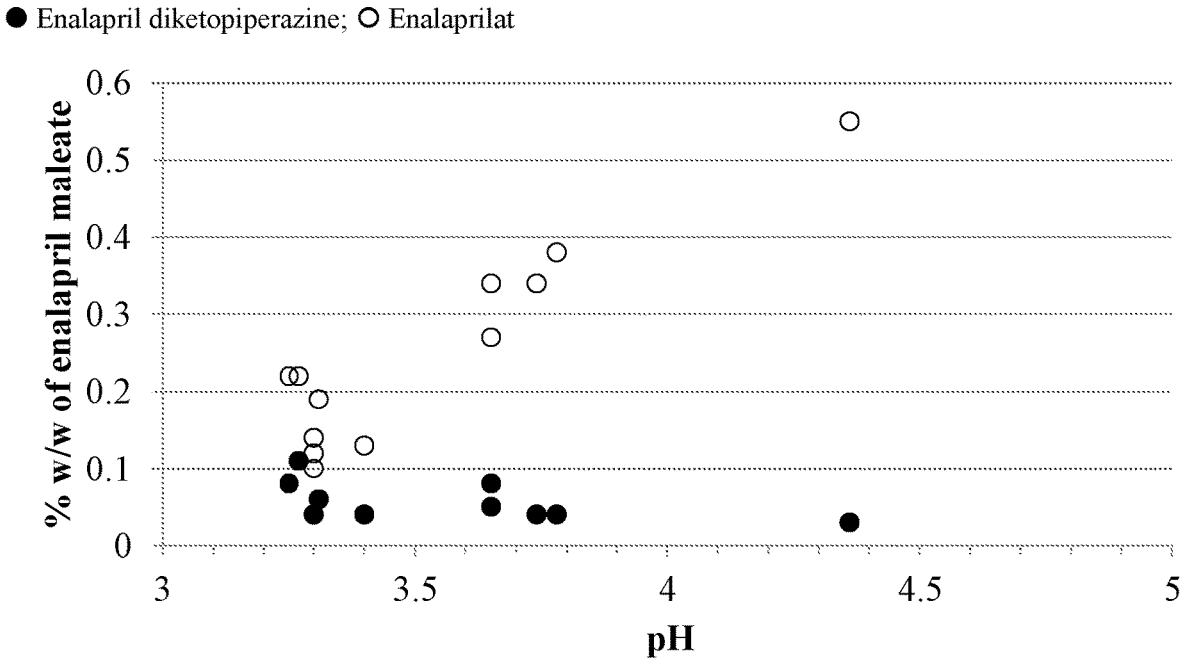
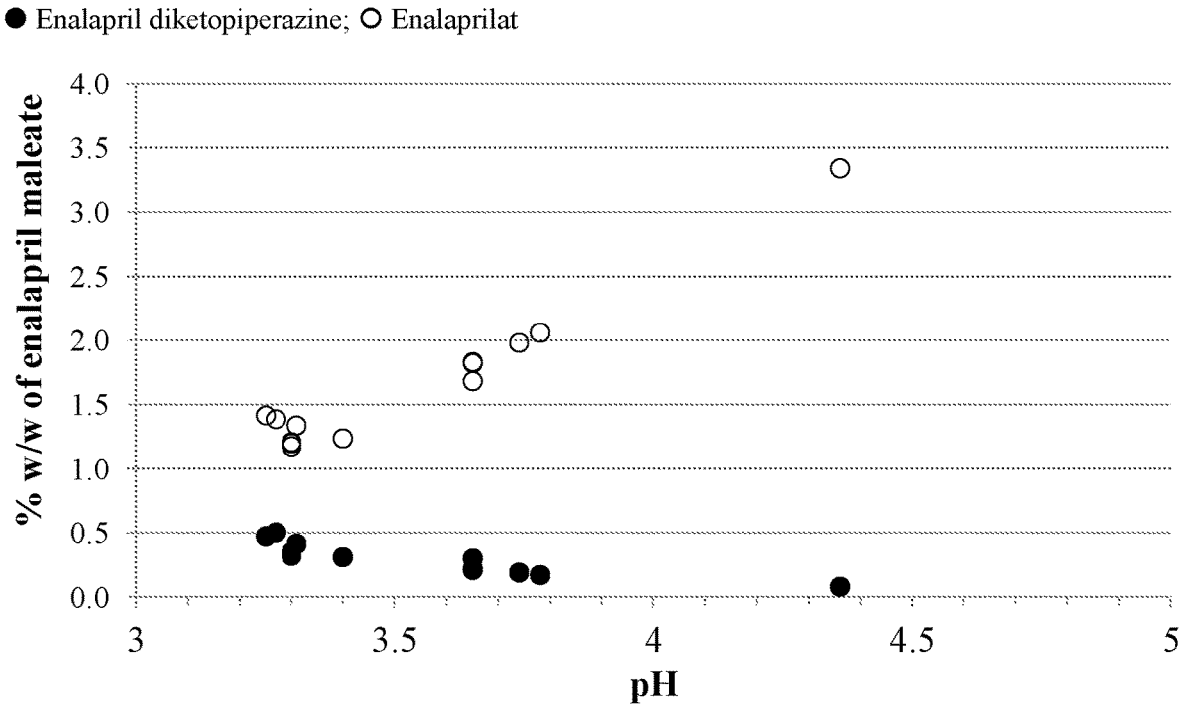

● Enalapril diketopiperazine; ○ Enalaprilat
% w/w of enalapril maleate
0.6
0.5
0.4
0.3
0.2
0.1
0
3
3.5
4
4.5
5
pH

FIG. 2


● Enalapril diketopiperazine; ○ Enalaprilat
% w/w of enalapril maleate
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
3
3.5
4
4.5
5
pH

ENALAPRIL FORMULATIONS

CROSS-REFERENCE OF RELATED APPLICATIONS

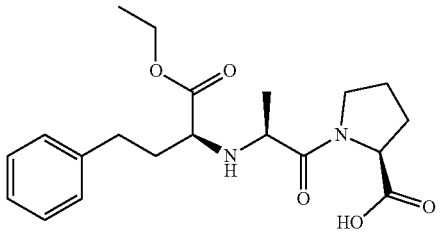
This application is a continuation of U.S. patent application Ser. No. 16/991,575, filed Aug. 12, 2020 which is a continuation of Ser. No. 16/883,553, filed May 26, 2020 which is a continuation of U.S. patent application Ser. No. 16/242,898, filed Jan. 8, 2019, which is a continuation of Ser. No. 16/177,159, filed Oct. 31, 2018, which is a continuation of U.S. patent application Ser. No. 16/003,994, filed Jun. 8, 2018 (now U.S. Pat. No. 10,154,987, issued Dec. 18, 2018), which is a continuation of U.S. patent application Ser. No. 15/802,341, filed Nov. 2, 2017 (now U.S. Pat. No. 10,039,745, issued Aug. 7, 2018), which is a continuation of U.S. patent application Ser. No. 15/613,622, filed Jun. 5, 2017 (now U.S. Pat. No. 9,808,442, issued Nov. 7, 2017), which is a continuation of U.S. patent application Ser. No. 15/081,603, filed Mar. 25, 2016 (now U.S. Pat. No. 9,669,008, issued Jun. 6, 2017), which claims the benefit of U.S. Provisional Patent Application No. 62/310,198, filed Mar. 18, 2016, all of which are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

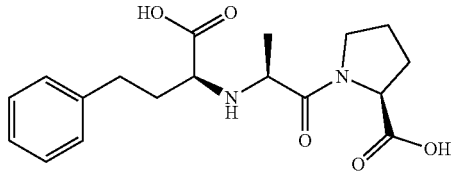
Hypertension, or high blood pressure, is a serious health issue in many countries. According to the National Heart Blood and Lung Institute, it is thought that about 1 in 3 adults in the United States alone have hypertension. Left unchecked, hypertension is considered a substantial risk factor for cardiovascular and other diseases including coronary heart disease, myocardial infarction, congestive heart failure, stroke and kidney failure. Hypertension is classified as primary (essential) hypertension or secondary hypertension. Primary hypertension has no known cause and may be related to a number of environmental, lifestyle and genetic factors such as stress, obesity, smoking, inactivity and sodium intake. Secondary hypertension can be caused by drug or surgical interventions, or by abnormalities in the renal, cardiovascular or endocrine system.

A number of antihypertensive drugs are available for treating hypertension. Various therapeutic classes of antihypertensive drugs include alpha-adrenergic blockers, beta-adrenergic blockers, calcium-channel blockers, hypotensives, mineralcorticoid antagonists, central alpha-agonists, diuretics and rennin-angiotensin-aldosterone inhibitors which include angiotensin II receptor antagonists (ARB) and angiotensin-converting enzyme (ACE) inhibitors. Angiotensin-converting enzyme (ACE) inhibitors inhibit angiotensin-converting enzyme (ACE), a peptydyl dipeptidase that catalyzes angiotension I to angiotension II, a potent vasoconstrictor involved in regulating blood pressure.

Enalapril is a prodrug belonging to the angiotensin-converting enzyme (ACE) inhibitor of medications. It is rapidly hydrolyzed in the liver to enalaprilat following oral administration. Enalaprilat acts as a potent inhibitor of ACE. The structural formulae of enalapril and enalaprilat are as follows:



Enalapril



Enalaprilat

Enalapril is currently administered in the form of oral tablets, (e.g., Vasotec®) or in the form of liquid formulations obtained by reconstitution of enalapril powder formulations. In addition to the treatment of hypertension, enalapril tablets have been used for symptomatic congestive heart failure, and asymptomatic left ventricular dysfunction.

SUMMARY OF THE INVENTION

Provided herein are enalapril oral liquid formulations. In one aspect, the enalapril oral liquid formulation, comprises (i) enalapril or a pharmaceutically acceptable salt or solvate thereof; (ii) a sweetener that is sucralose (iii) a buffer comprising citric acid; (iv) a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5±3° C. for at least 12 months.

In some embodiments, the enalapril is enalapril maleate. In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer in the formulation further comprises sodium citrate dihydrate. In some embodiments, the amount of enalapril or a pharmaceutically acceptable salt or solvate thereof is about 0.6 to about 1.2 mg/ml. In some embodiments, the amount of sucralose is about 0.5 to about 0.9 mg/ml. In some embodiments, the amount of citric acid in the buffer is about 0.8 to about 3.5 mg/ml. In some embodiments, the amount of sodium citrate dihydrate in the buffer is about 0.1 to about 0.80 mg/ml. In some embodiments, the amount of the sodium benzoate is about 0.2 to about 1.2 mg/ml. In some embodiments, the amount of enalapril or a pharmaceutically acceptable salt or solvate thereof is about 10 to about 25% (w/w of solids). In some embodiments, the amount of sucralose is about 8 to about 18% (w/w of solids). In some embodiments, the amount of citric acid in the buffer is about 17 to about 47% (w/w of solids). In some embodiments, the amount of sodium citrate dihydrate in the buffer is about 1 to about 11% (w/w of solids). In some embodiments, the amount of sodium benzoate is about 12 to about 25% (w/w of solids). In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about 5±3° C. for at least 18 months.

In some embodiments, the formulation is stable at about 5±3° C. for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In one aspect, the enalapril oral liquid formulation, comprises (i) about 1 mg/ml enalapril maleate; (ii) about 0.70 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5±3° C. for at least 12 months.

In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer further comprises about 0.15 mg/mL sodium citrate dihydrate. In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about 5±3° C. for at least 18 months. In some embodiments, the formulation is stable at about 5±3° C. for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In one aspect, the enalapril oral liquid formulation comprises (i) about 19.3% (w/w of solids) enalapril maleate; (ii) about 13.5% (w/w of solids) of a sweetener that is sucralose; (iii) a buffer comprising about 35.2% (w/w of solids) citric acid; (iv) about 19.3% (w/w of solids) of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5±3° C. for at least 12 months.

In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer further comprises about 2.9% (w/w of solids) sodium citrate dihydrate. In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about 5±3° C. for at least 18 months. In some embodiments, the formulation is stable at about 5±3° C. for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In one aspect, the enalapril oral liquid formulation consists essentially of (i) about 1 mg/m enalapril maleate; (ii) about 0.70 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; (v) a flavoring agent; and (vi) water; wherein the pH of the formulation is less than about 3.5 adjusted by sodium hydroxide or hydrochloric acid; and wherein the formulation is stable at about 5±3° C. for at least 12 months.

Also provided herein are methods of treating hypertension in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.7 mg/ml sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5±3° C. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In some embodiments, the hypertension is primary (essential) hypertension. In some embodiments, the hypertension is secondary hypertension. In some embodiments, the subject has blood pressure values greater than or equal to 140/90 mmm Hg. In some embodiments, the subject is an adult. In some embodiments, the subject is elderly. In some embodiments, the subject is a child. In some embodiments, the formulation is administered to the subject in a fasted state. In some embodiments, the formulation is administered to the subject in a fed state. In some embodiments, the formulation is further administered in combination with an agent selected from the group consisting of diuretics, beta blockers, alpha blockers, mixed alpha and beta blockers, calcium channel blockers, angiotensin II receptor antagonists, ACE inhibitors, aldosterone antagonists, and alpha-2 agonists.

Also provided herein are methods of treating prehypertension in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.7 mg/ml of a sweetener that is sucralose; (ii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5±3° C. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In some embodiments, the subject has blood pressure values of about 120-139/80-89 mm Hg.

Also provided herein are methods of treating heart failure in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.70 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5±3° C. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

Also provided herein are methods of treating left ventricular dysfunction in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.7 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5±3° C. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

INCORPORATION BY REFERENCE

All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication,

patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

FIG. **1**: Effect of pH on degradant formation after 8 weeks of storage of various enalapril solution formulations at 5° C.

FIG. **2**: Effect of pH on degradant formation after 8 weeks of storage of various enalapril solution formulations at room temperature (19-22° C.).

DETAILED DESCRIPTION OF THE INVENTION

Provided herein are stable enalapril oral liquid formulations. Also provided herein are stable enalapril powder formulations for reconstitution for oral liquid administration. These enalapril formulations described herein are useful for the treatment of hypertension, prehypertension, heart failure as well as ventricular dysfunction. The formulations are advantageous over conventional solid dosage administration of enalapril ranging from ease of administration, accuracy of dosing, accessibility to additional patient populations such as to children and the elderly, and an increased patient compliance to medication.

It is generally known that certain segments of the population have difficulty ingesting and swallowing solid oral dosage forms such as tablets and capsules. As many as a quarter of the total population has this difficulty. Often, this leads to non-compliance with the recommended medical therapy with the solid dosage forms, thereby resulting in rending the therapy ineffective. Further, solid dosage forms are not recommended for children or elderly due to increased risk in choking.

Furthermore, the dose of enalapril to be given to children is calculated according to the child's weight. When the calculated dose is something other than the amount present in one or more intact solid dosage forms, the solid dosage form must be divided to provide the correct dose. This leads to inaccurate dosing when solid dosages forms, such as tablets, are compounded to prepare other formulations for children.

For enalapril, one solution to overcoming the use of the tablet form is for a compounding pharmacist to pulverize and crush the enalapril tablet(s) into a powder via mortar and pestle and reconstitute the powder in some liquid form. However forming a enalapril oral liquid in this fashion has significant drawbacks including large variability in the actual dosage, incomplete solubilizing of the enalapril tablet in the liquid, rapid instability, inconsistent formulation methods per compounding pharmacy, and a number of other potential issues. The crushed tablet liquid formulation may also be potentially unsafe due to contamination with residual drugs and other substances from the mortar and pestle or other crushing agent.

Alternatively, enalapril is formulated as enalapril powder compositions for reconstitution as oral liquids as described in U.S. Pat. No. 8,568,747. The powder compositions as described in this patent require mannitol and colloidal silicon dioxide for stability and dissolution. While these powder compositions are an improvement over crushing tablets, they still require a step of mixing with a diluent. The stable enalapril oral liquid formulations described herein require no extra steps or manipulation prior to administration to a subject. Further, the stable enalapril oral liquid formulations described herein do not require or need mannitol or colloidal silicon dioxide for stability and dissolution.

The present embodiments described herein provide a safe and effective oral administration of enalapril for the treatment of hypertension and other disorders. In particular, the embodiments provide stable enalapril oral liquid formulations as well as alternatively enalapril powder formulations for oral liquid administration.

As used herein, "enalapril" refers to enalapril base, its salt, or solvate or derivative or isomer or polymorph thereof. Suitable compounds include the free base, the organic and inorganic salts, isomers, isomer salts, solvates, polymorphs, complexes etc. U.S. Pat. Nos. 4,374,829; 4,472,380 and 4,510,083 disclose exemplary methods in the preparation of enalapril. In some embodiments, the enalapril used in the formulations described herein is an enalapril salt. In some instances, the enalapril salt is enalapril maleate. In other instances, the enalapril salt is in the form of enalapril sodium.

Other ACE inhibitors are contemplated in the formulations within and include but are not limited to quinapril, indolapril, ramipril, perindopril, lisinopril, benazepril, imidapril, zofenopril, trandolapril, fosinopril, captopril, and their salts, solvates, derivatives, polymorphs, or complexes, thereof.

Enalapril Oral Liquid Formulations

Oral liquids include, but are not limited to, solutions (both aqueous and nonaqueous), suspensions, emulsions, syrups, slurries, juices, elixirs, dispersions, and the like. It is envisioned that solution/suspensions are also included where certain components described herein are in a solution while other components are in a suspension.

In one aspect, the enalapril liquid formulations described herein comprise enalapril, a preservative, a sweetening agent, a buffer, and water. In one embodiment, the sweetening agent is sucralose. In one embodiment, the sweetening agent is xylitol. In one embodiment, the sweetening agent is not mannitol. In another embodiment, the preservative is sodium benzoate. In some embodiments, the preservative is a paraben. In some embodiments, the preservative is a mixture of parabens. In yet another embodiment, the buffer comprises citric acid. In some embodiments, the buffer further comprises sodium citrate. In one aspect, the enalapril liquid formulation described herein comprises enalapril, sucralose, sodium benzoate, citric acid, sodium citrate, and water. In some embodiments, the enalapril liquid formulation herein further comprises a flavoring agent. In some embodiments, the enalapril liquid formulation is not obtained from crushing enalapril tablet and dissolving the powder in a suitable vehicle for oral administration. In some embodiments, the enalapril liquid formulation does not contain silicon dioxide. In some embodiments, the enalapril liquid formulation does not contain mannitol. In some embodiments, the enalapril liquid formulation does not contain lactose. In some embodiments, the enalapril liquid formulation does not contain magnesium stearate. In some embodiments, the enalapril liquid formulation does not contain sodium bicarbonate. In some embodiments, the enalapril liquid formulation does not contain iron oxides.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.6 to about 1.2 mg/ml in the oral liquid formulation. In other embodiments,

enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/ml, about 0.91 mg/ml, about 0.92 mg/ml, about 0.93 mg/ml, about 0.94 mg/ml, about 0.95 mg/ml, about 0.96 mg/ml, about 0.97 mg/ml, about 0.98 mg/ml, about 0.99 mg/ml, about 1 mg/ml, about 1.01 mg/ml, about 1.02, mg/ml, about 1.03 mg/ml, about 1.04 mg/ml, about 1.05 mg/ml, about 1.06 mg/ml, about 1.07 mg/ml, about 1.08 mg/ml, about 1.09 mg/ml, about 1.1 mg/ml, about 1.11 mg/ml, about 1.12, mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, or about 1.2 mg/ml in the liquid oral formulation. In some embodiments, enalapril is present in about 0.76 mg/ml in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 1 mg/ml in the oral liquid formulation. In some embodiments, the formulation contains enalapril or another pharmaceutically acceptable salt of enalapril in a molar concentration equivalent to 1 mg/mL enalapril maleate. In some embodiments, the formulation contains enalapril or another pharmaceutically acceptable salt of enalapril in a molar concentration equivalent to 0.76 mg/mL enalapril.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w to about 30% w/w of the solids in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w, about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about 15.1% w/w, about 15.2% w/w, about 15.3% w/w, about 15.4% w/w, about 15.5% w/w, about 15.6% w/w, about 15.7% w/w, about 15.8% w/w, about 15.9% w/w, about 16% w/w, about 16.1% w/w, about 16.2% w/w, about 16.3% w/w, about 16.4% w/w, about 16.5% w/w, about 16.6% w/w, about 16.7% w/w, about 16.8% w/w, about 16.9% w/w, about 17% w/w, about 17.1% w/w, about 17.2% w/w, about 17.3% w/w, about 17.4% w/w, about 17.5% w/w, about 17.6% w/w, about 17.7% w/w, about 17.8% w/w, about 17.9% w/w, about 18% w/w, about 18.1% w/w, about 18.2% w/w, about 18.3% w/w, about 18.4% w/w, about 18.5% w/w, about 18.6% w/w, about 18.7% w/w, about 18.8% w/w, about 18.9% w/w, about 19% w/w, about 19.1% w/w, about 19.2% w/w, about 19.3% w/w, about 19.4% w/w, about 19.5% w/w, about 19.6% w/w, about 19.7% w/w, about 19.8% w/w, about 19.9% w/w, about 20% w/w, about 20.1% w/w, about 20.2% w/w, about 20.3% w/w, about 20.4% w/w, about 20.5% w/w, about 20.6% w/w, about 20.7% w/w, about 20.8% w/w, about 20.9% w/w, about 21% w/w, about 21.1% w/w, about 21.2% w/w, about 21.3% w/w, about 21.4% w/w, about 21.5% w/w, about 21.6% w/w, about 21.7% w/w, about 21.8% w/w, about 21.9% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5% w/w, about 25% w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 10% w/w to about 25% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 10.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 15% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 18.2% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 13.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 19.3% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 24.5% w/w of the solids in the oral liquid formulation.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w to about 1% w/w of the solids in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w, about 0.15% w/w, about 0.2% w/w, about 0.25% w/w, about 0.3% w/w, about 0.35% w/w, about 0.4% w/w, about 0.45% w/w, about 0.5% w/w, about 0.55% w/w, about 0.6% w/w, about 0.65% w/w, about 0.7% w/w, about 0.75% w/w, about 0.8% w/w, about 0.85% w/w, about 0.9% w/w, about 0.95% w/w, or about 1% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.4% w/w to about 0.7% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 0.4% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 0.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 0.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 0.6% w/w of the solids in the oral liquid formulation.

Sweetener in the Enalapril Oral Liquid Formulations

Sweeteners or sweetening agents include any compounds that provide a sweet taste. This includes natural and synthetic sugars, natural and artificial sweeteners, natural extracts and any material that initiates a sweet sensation in a subject. In some embodiments, a solid/powder sweetener is used in the oral liquid formulation described herein. In other embodiments, a liquid sweetener is used in the oral liquid formulation described herein.

Sugars illustratively include glucose, fructose, sucrose, xylitol, tagatose, sucralose, maltitol, isomaltulose, Isomalt™ (hydrogenated isomaltulose), lactitol, sorbitol, erythritol, trehalose, maltodextrin, polydextrose, and the like. Other sweeteners illustratively include glycerin, inulin, erythritol, maltol, acesulfame and salts thereof, e.g., acesulfame potassium, alitame, aspartame, neotame, sodium cyclamate, saccharin and salts thereof, e.g., saccharin sodium or saccharin calcium, neohesperidin dihydrochalcone, stevioside, thaumatin, and the like. Sweeteners can be used in the form of crude or refined products such as hydrogenated starch hydrolysates, maltitol syrup, high fructose corn syrup, etc., and as branded products, e.g., Sweet Am™ liquid (Product Code 918.003-propylene glycol, ethyl alcohol, and proprietary artificial flavor combination, Flavors of North

America) and Sweet Am™ powder (Product Code 918.005-maltodextrin, sorbitol, and fructose combination and Product Code 918.010-water, propylene glycol, sorbitol, fructose, and proprietary natural and artificial flavor combination, Flavors of North America), ProSweet™ (1-10% proprietary plant/vegetable extract and 90-99% dextrose combination, Viriginia Dare), Maltisweet™ (maltitol solution, Ingredion), Sorbo™ (sorbitol and sorbitol/xylitol solution, SPI Polyols), Invertose™ (high fructose corn syrup, Ingredion), Rebalance M60 and X60 (sucralose and maltodextrin, Tate and Lyle), and Ora-Sweet™ sugar-free flavored syrup (Paddock Laboratories, Inc.). Sweeteners can be used singly or in combinations of two or more. Suitable concentrations of different sweeteners can be selected based on published information, manufacturers' data sheets and by routine testing.

In some embodiments, the enalapril oral liquid formulation described herein comprises a sweetening agent. In some embodiments, the sweetening agent is sucralose. In some embodiments, the sweetening agent is xylitol. In some embodiments, the sweetener is not mannitol.

In some embodiments, the enalapril oral liquid formulation described herein comprises sucralose. In some embodiments, sucralose is present in about 0.5 to about 0.9 mg/ml in the oral liquid formulation.

In other embodiments, sucralose is present in about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml, about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.60 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.70 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.80 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, or about 0.90 mg/ml in the oral liquid formulation. In some embodiments, sucralose is present in about 0.7 mg/ml in the oral liquid formulation.

In some embodiments, sucralose is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about 15.5% w/w, about 16% w/w, about 16.5% w/w, about 17% w/w, about 17.5% w/w, about 18% w/w, about 18.5% w/w, about 19% w/w, about 19.5% w/w, about 20% w/w, about 20.5% w/w, about 21% w/w, about 21.5% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5% w/w, about 25% w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 8% w/w to about 18% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 9.5% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 13.5% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 16.5% w/w of the solids in the oral liquid formulation.

In some embodiments, the enalapril oral liquid formulation described herein comprises xylitol. In some embodiments, xylitol is present in about 140 mg/ml to about 210 mg/ml in the oral liquid formulation.

In some embodiments, xylitol is present in about 140 mg/ml, about 145 mg/ml, about 150 mg/ml, about 155 mg/ml, about 160 mg/ml, about 165 mg/ml, about 170 mg/ml, about 175 mg/ml, about 180 mg/ml, about 185 mg/ml, about 190 mg/ml, about 195 mg/ml, about 200 mg/ml, about 205 mg/ml, or about 210 mg/ml of the oral liquid formulation. In some embodiments, xylitol is present in about 150 mg/ml in the oral liquid formulation. In some embodiments, xylitol is present in about 200 mg/ml in the oral liquid formulation.

In some embodiments, xylitol is present in about 80% w/w to about 99% w/w of the solids in the oral liquid formulation. In other embodiments, xylitol is present in about 80% w/w, about 81% w/w, about 82% w/w, about 83% w/w, about 84% w/w, about 85% w/w, about 86% w/w, about 87% w/w, about 88% w/w, about 89% w/w, about 90% w/w, about 91% w/w, about 92% w/w, about 93% w/w, about 94% w/w, about 95% w/w, about 96% w/w, about 97% w/w, about 98% w/w, or about 99% w/w of the solids in the oral liquid formulation. In some embodiments, xylitol is present in about 96% w/w to about 98% w/w of the solids in the oral liquid formulation. In some embodiments, xylitol is present in about 96% w/w of the solids in the oral liquid formulation.

Preservative in the Enalapril Oral Liquid Formulations

Preservatives include anti-microbials, anti-oxidants, and agents that enhance sterility. Exemplary preservatives include ascorbic acid, ascorbyl palmitate, BHA, BHT, citric acid, EDTA and its salts, erythorbic acid, fumaric acid, malic acid, propyl gallate, sodium ascorbate, sodium bisulfate, sodium metabisulfite, sodium sulfite, parabens (such as methylparaben, ethylparaben, propylparaben, butylparaben and their salts), benzoic acid, sodium benzoate, potassium sorbate, vanillin, and the like.

In some embodiments, the enalapril oral liquid formulation described herein comprises a preservative.

In some embodiments, the preservative is a paraben and the sweetener is not a sugar (such as, but not limited to glucose, fructose, sucrose, lactose, maltose) or a sugar alcohol (such as, but not limited to xylitol, mannitol, lactitol, maltitol, sorbitol).

In some embodiments, the preservative is sodium benzoate.

In some embodiments, modulation of the pH is desired to provide the best antimicrobial activity of the preservative, sodium benzoate. In some embodiments, the antimicrobial activity of sodium benzoate drops when the pH is increased above 5.

In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about

3.9, or about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3.3.

In some embodiments, sodium benzoate is present in about 0.2 to about 1.2 mg/ml in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 0.2 mg/ml, about 0.21 mg/ml, about 0.22 mg/ml, about 0.23 mg/ml, about 0.24 mg/ml, about 0.25 mg/ml, about 0.26 mg/ml, about 0.27 mg/ml, about 0.28 mg/ml, about 0.29 mg/ml, about 0.3 mg/ml, about 0.31 mg/ml, about 0.32 mg/ml, about 0.33 mg/ml, about 0.34 mg/ml, about 0.35 mg/ml, about 0.36 mg/ml, about 0.37 mg/ml, about 0.38 mg/ml, about 0.39 mg/ml, about 0.4 mg/ml, about 0.41 mg/ml, about 0.42 mg/ml, about 0.43 mg/ml, about 0.44 mg/ml, about 0.45 mg/ml, about 0.46 mg/ml, about 0.47 mg/ml, about 0.48 mg/ml, about 0.49 mg/ml, about 0.5 mg/ml, about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml, about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/ml, about 0.91 mg/ml, about 0.92 mg/ml, about 0.93 mg/ml, about 0.94 mg/ml, about 0.95 mg/ml, about 0.96 mg/ml, about 0.97 mg/ml, about 0.98 mg/ml, about 0.99 mg/ml, about 1 mg/ml, about 1.01 mg/ml, about 1.02, mg/ml, about 1.03 mg/ml, about 1.04 mg/ml, about 1.05 mg/ml, about 1.06 mg/ml, about 1.07 mg/ml, about 1.08 mg/ml, about 1.09 mg/ml, about 1.1 mg/ml, about 1.11 mg/ml, about 1.12, mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, or about 1.2 mg/ml in the liquid oral formulation. In some embodiments, sodium benzoate is present in about 1 mg/ml in the oral liquid formulation.

In some embodiments, sodium benzoate is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about 15.1% w/w, about 15.2% w/w, about 15.3% w/w, about 15.4% w/w, about 15.5% w/w, about 15.6% w/w, about 15.7% w/w, about 15.8% w/w, about 15.9% w/w, about 16% w/w, about 16.1% w/w, about 16.2% w/w, about 16.3% w/w, about 16.4% w/w, about 16.5% w/w, about 16.6% w/w, about 16.7% w/w, about 16.8% w/w, about 16.9% w/w, about 17% w/w, about 17.1% w/w, about 17.2% w/w, about 17.3% w/w, about 17.4% w/w, about 17.5% w/w, about 17.6% w/w, about 17.7% w/w, about 17.8% w/w, about 17.9% w/w, about 18% w/w, about 18.1% w/w, about 18.2% w/w, about 18.3% w/w, about 18.4% w/w, about 18.5% w/w, about 18.6% w/w, about 18.7% w/w, about 18.8% w/w, about 18.9% w/w, about 19% w/w, about 19.1% w/w, about 19.2% w/w, about 19.3% w/w, about 19.4% w/w, about 19.5% w/w, about 19.6% w/w, about 19.7% w/w, about 19.8% w/w, about 19.9% w/w, about 20% w/w, about 20.1% w/w, about 20.2% w/w, about 20.3% w/w, about 20.4% w/w, about 20.5% w/w, about 20.6% w/w, about 20.7% w/w, about 20.8% w/w, about 20.9% w/w, about 21% w/w, about 21.1% w/w, about 21.2% w/w, about 21.3% w/w, about 21.4% w/w, about 21.5% w/w, about 21.6% w/w, about 21.7% w/w, about 21.8% w/w, about 21.9% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5% w/w, about 25% w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 10% w/w to about 25% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 13.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 19.3% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 23.5% w/w of the solids in the oral liquid formulation.

In some embodiments, sodium benzoate is present in about 0.1% w/w to about 1% w/w of the solids in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 0.1% w/w, about 0.15% w/w, about 0.2% w/w, about 0.25% w/w, about 0.3% w/w, about 0.35% w/w, about 0.4% w/w, about 0.45% w/w, about 0.5% w/w, about 0.55% w/w, about 0.6% w/w, about 0.65% w/w, about 0.7% w/w, about 0.75% w/w, about 0.8% w/w, about 0.85% w/w, about 0.9% w/w, about 0.95% w/w, or about 1% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.4% w/w to about 0.7% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.45% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.6% w/w of the solids in the oral liquid formulation.

In some embodiments, sodium benzoate is present in an amount sufficient to provide antimicrobial effectiveness to the enalapril oral liquid formulation described herein. (See Table G-1).

In some embodiments, the preservative is a paraben. In some embodiments, the preservative is a mixture of parabens. In some embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml to about 2 mg/ml in the oral liquid formulation. In other embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml, about 0.2 mg/ml, about 0.3 mg/ml, about 0.4 mg/ml, about 0.5 mg/ml, about 0.6 mg/ml, about 0.7 mg/ml, about 0.8 mg/ml, about 0.9 mg/ml, about 1 mg/ml, about 1.1 mg/ml, about 1.2 mg/ml, about 1.3 mg/ml, about 1.4 mg/ml, or about 1.5 mg/ml, about 1.6 mg/ml, about 1.7 mg/ml, about 1.8 mg/ml, about 1.9 mg/ml, or about 2 mg/ml in the liquid oral formulation. In some embodiments, the paraben or mixture of parabens is present in about 1.6 mg/ml to about 2 mg/ml in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 1.6 mg/ml to about 1.8 mg/ml in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml to about 0.5 mg/ml in the oral liquid formulation.

In some embodiments, the paraben or mixture of parabens is present in about 2% w/w to about 30% w/w of the solids in the oral liquid formulation. In other embodiments, the paraben or mixture of parabens is present in about 2% w/w,

about 3% w/w, about 4% w/w, about 5% w/w, about 6% w/w, about 7% w/w, about 8% w/w, about 9% w/w, about 10% w/w, about 11% w/w, about 12% w/w, about 13% w/w, about 14% w/w, about 15% w/w, about 16% w/w, about 17% w/w, about 18% w/w, about 19% w/w, about 20% w/w, about 21% w/w, about 22% w/w, about 23% w/w, about 24% w/w, about 25% w/w, about 26% w/w, about 27% w/w, about 28% w/w, about 29% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 2% w/w to about 3% w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 23% w/w to about 26% w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 26% w/w to about 30% w/w of the solids in the oral liquid formulation.

Sweetener and Preservative Incompatibility

Paraben preservatives (especially methylparaben) can react with selected sugars (glucose, fructose, sucrose, lactose, maltose) and sugar alcohols (xylitol, mannitol, lactitol, maltitol, sorbitol) to form transesterification reaction products. This can be undesirable from a formulation and stability standpoint as the transesterification creates additional degradants.

In some embodiments, the enalapril oral liquid formulation described herein does not comprise a paraben preservative. In further embodiments, the enalapril oral liquid formulation described herein does not comprise a paraben preservative when the formulation also comprises a sugar or sugar alcohol.

pH of Enalapril Oral Liquid Formulations

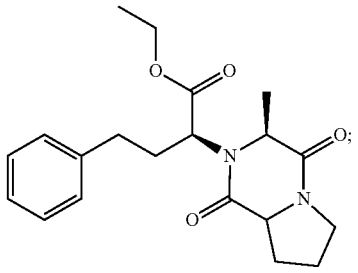
Buffering agents maintain the pH of the liquid enalapril formulation. Non-limiting examples of buffering agents include, but are not limited to sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium glucomate, aluminum hydroxide, aluminum hydroxide/sodium bicarbonate co-precipitate, mixture of an amino acid and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer. Additional buffering agents include citric acid, sodium citrate, sodium tartarate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, sodium acetate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, and other calcium salts. Some buffering agents also impart effervescent qualities when a powder is reconstituted in a solution. In some embodiments, the buffering agent is not sodium bicarbonate.

In some embodiments, the oral liquid formulation comprises a buffer.

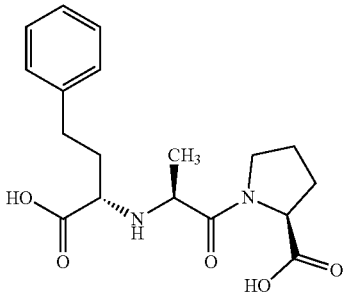
In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid and sodium citrate. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid and sodium citrate dihydrate or an equivalent molar amount of sodium citrate anhydrous. In some embodiments, the sodium citrate is monosodium citrate. In some embodiments, the sodium citrate is disodium citrate. In some embodiments, the sodium citrate is trisodium citrate.

In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises phosphoric acid. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises sodium phosphate.

In some embodiments, modulation of the pH is desired to provide a lowered impurity profile. In the exemplary stability studies, the main enalapril degradants are enalapril diketopiperazine and enalaprilat:



enalapril diketopiperazine



enalaprilat

In some embodiments, the percentage of enalaprilat formation is increased when the pH is above 3.5. (See table C-2 and FIG. **1** and FIG. **2**). In some embodiments, the percentage of enalapril diketopiperazine formation is slightly increased as the pH is below 4.

In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, or about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3.3.

In some embodiments, the formation of degradants is dependent on the buffer concentration. In some embodiments, the buffer concentration impacts the taste of the enalapril oral liquid formulation.

In some embodiments, the buffer concentration is between about 5 mM and about 20 mM. In some embodiments, the buffer concentration is about 5 mM, about 6 mM, about 7 mM, about 8 mM, about 9 mM, about 10 mM, about

11 mM, about 12 mM, about 13 mM, about 14 mM, about 15 mM, about 16 mM, about 17 mM, about 18 mM, about 19 mM, or about 20 mM. In some embodiments, the buffer concentration is about 5 mM. In some embodiments, the buffer concentration is about 10 mM. In some embodiments, the buffer concentration is about 20 mM.

In some embodiments, citric acid is present in about 0.7 to about 2 mg/ml in the oral liquid formulation. In other embodiments, citric acid is present in about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/mL, about 0.91 mg/mL, about 0.92 mg/mL, about 0.93 mg/mL, about 0.94 mg/mL, about 0.95 mg/mL, about 0.96 mg/mL, about 0.97 mg/mL, about 0.98 mg/mL, about 0.99 mg/mL, about 1 mg/mL, about 1.11 mg/ml, about 1.12 mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, about 1.2 mg/ml, about 1.21 mg/ml, about 1.22 mg/ml, about 1.23 mg/ml, about 1.24 mg/ml, about 1.25 mg/ml, about 1.26 mg/ml, about 1.27 mg/ml, about 1.28 mg/ml, about 1.29 mg/ml, about 1.3 mg/mL, about 1.31 mg/mL, about 1.32 mg/mL, about 1.33 mg/mL, about 1.34 mg/mL, about 1.35 mg/mL, about 1.36 mg/mL, about 1.37 mg/mL, about 1.38 mg/mL, about 1.39 mg/mL, about 1.4 mg/ml, about 1.41 mg/ml, about 1.42 mg/ml, about 1.43 mg/ml, about 1.44 mg/ml, about 1.45 mg/ml, about 1.46 mg/ml, about 1.47 mg/ml, about 1.48 mg/ml, about 1.49 mg/ml, about 1.5 mg/ml, about 1.51 mg/ml, about 1.52 mg/ml, about 1.53 mg/ml, about 1.54 mg/ml, about 1.55 mg/ml, about 1.56 mg/ml, about 1.57 mg/ml, about 1.58 mg/ml, about 1.59 mg/ml, about 1.6 mg/mL, about 1.61 mg/mL, about 1.62 mg/mL, about 1.63 mg/mL, about 1.64 mg/mL, about 1.65 mg/mL, about 1.66 mg/mL, about 1.67 mg/mL, about 1.68 mg/mL, about 1.69 mg/mL, about 1.7 mg/ml, about 1.71 mg/ml, about 1.72 mg/ml, about 1.73 mg/ml, about 1.74 mg/ml, about 1.75 mg/ml, about 1.76 mg/ml, about 1.77 mg/ml, about 1.78 mg/ml, about 1.79 mg/ml, about 1.8 mg/ml, about 1.81 mg/ml, about 1.82 mg/ml, about 1.83 mg/ml, about 1.84 mg/ml, about 1.85 mg/ml, about 1.86 mg/ml, about 1.87 mg/ml, about 1.88 mg/ml, about 1.89 mg/ml, about 1.9 mg/mL, about 1.91 mg/mL, about 1.92 mg/mL, about 1.93 mg/mL, about 1.94 mg/mL, about 1.95 mg/mL, about 1.96 mg/mL, about 1.97 mg/mL, about 1.98 mg/mL, about 1.99 mg/mL, or about 2 mg/mL in the oral liquid formulation. In some embodiments, citric acid is present in about 1.65 mg/ml in the oral liquid formulation. In some embodiments, citric acid is present in about 1.82 mg/ml in the oral liquid formulation. In some embodiments, citric acid is present in about 0.82 mg/ml in the oral liquid formulation.

In some embodiments, citric acid is present in about 2 to about 3.5 mg/ml in the oral liquid formulation. In other embodiments, citric acid is present in about 2 mg/mL, about 2.05 mg/mL, about 2.1 mg/mL, about 2.15 mg/mL, about 2.2 mg/mL, about 2.25 mg/mL, about 2.3 mg/mL, about 2.35 mg/mL, about 2.4 mg/mL, about 2.45 mg/mL, about 2.5 mg/mL, about 2.55 mg/mL, about 2.6 mg/mL, about 2.65 mg/mL, about 2.7 mg/mL, about 2.75 mg/mL, about 2.8 mg/mL, about 2.85 mg/mL, about 2.9 mg/mL, about 2.95 mg/mL, about 3 mg/mL, about 3.05 mg/ml, about 3.1 mg/mL, about 3.15 mg/mL, about 3.2 mg/mL, about 3.25 mg/mL, about 3.3 mg/mL, about 3.35 mg/mL, about 3.4 mg/mL, about 3.45 mg/mL, or about 3.5 mg/mL in the oral liquid formulation. In some embodiments, citric acid is present in about 3.3 mg/ml in the oral liquid formulation.

In some embodiments, citric acid is present in about 10% w/w to about 50% w/w of the solids in the oral liquid formulation. In other embodiments, citric acid is present in about 10% w/w, about 11% w/w, about 12% w/w, about 13% w/w, about 14% w/w, about 15% w/w, about 16% w/w, about 17% w/w, about 18% w/w, about 19% w/w, about 20% w/w, about 21% w/w, about 22% w/w, about 23% w/w, about 24% w/w, about 25% w/w, about 26% w/w, about 27% w/w, about 28% w/w, about 29% w/w, about 30% w/w, about 31% w/w, about 32% w/w, about 33% w/w, about 34% w/w, about 35% w/w, about 36% w/w, about 37% w/w, about 38% w/w, about 39% w/w, about 40% w/w, about 41% w/w, about 42% w/w, about 43% w/w, about 44% w/w, about 45% w/w, about 46% w/w, about 47% w/w, about 48% w/w, about 49% w/w, about 50% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 45% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 31% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 35% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 19% w/w of the solids in the oral liquid formulation.

In some embodiments, citric acid is present in about 1% w/w to about 5% w/w of the solids in the oral liquid formulation. In other embodiments, citric acid is present in about 1% w/w, about 1.1% w/w, about 1.2% w/w, about 1.3% w/w, about 1.4% w/w, about 1.5% w/w, about 1.6% w/w, about 1.7% w/w, about 1.8% w/w, about 1.9% w/w, about 2% w/w, about 2.1% w/w, about 2.2% w/w, about 2.3% w/w, about 2.4% w/w, about 2.5% w/w, about 2.6% w/w, about 2.7% w/w, about 2.8% w/w, about 2.9% w/w, about 3% w/w, about 3.1% w/w, about 3.2% w/w, about 3.3% w/w, about 3.4% w/w, about 3.5% w/w, about 3.6% w/w, about 3.7% w/w, about 3.8% w/w, about 3.9% w/w, about 4% w/w, about 4.1% w/w, about 4.2% w/w, about 4.3% w/w, about 4.4% w/w, about 4.5% w/w, about 4.6% w/w, about 4.7% w/w, about 4.8% w/w, about 4.9% w/w, or about 5% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 2.1% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 1.6% w/w of the solids in the oral liquid formulation.

In some embodiments, sodium citrate dihydrate is present in about 0.1 to about 0.8 mg/ml in the oral liquid formulation. In other embodiments, sodium citrate dihydrate is present in the oral liquid formulation is about 0.1 mg/mL, about 0.11 mg/mL, about 0.12 mg/mL, about 0.13 mg/mL, about 0.14 mg/mL, about 0.15 mg/ml, about 0.16 mg/mL, about 0.17 mg/mL, about 0.18 mg/mL, about 0.19 mg/mL, about 0.2 mg/ml, about 0.21 mg/ml, about 0.22 mg/ml, about 0.23 mg/ml, about 0.24 mg/ml, about 0.25 mg/ml, about 0.26 mg/ml, about 0.27 mg/ml, about 0.28 mg/ml, about 0.29 mg/ml, about 0.3 mg/ml, about 0.31 mg/ml, about 0.32 mg/ml, about 0.33 mg/ml, about 0.34 mg/ml, about 0.35 mg/ml, about 0.36 mg/ml, about 0.37 mg/ml, about 0.38 mg/ml, about 0.39 mg/ml, about 0.4 mg/ml, about 0.41 mg/ml, about 0.42 mg/ml, about 0.43 mg/ml, about 0.44 mg/ml, about 0.45 mg/ml, about 0.46 mg/ml, about 0.47 mg/ml, about 0.48 mg/ml, about 0.49 mg/ml, about 0.5 mg/ml, about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml, about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.6 mg/ml, about 0.61 mg/ml,

about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, or about 0.8 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.75 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.35 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.2 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.15 mg/ml in the oral liquid formulation.

In some embodiments, sodium citrate dihydrate is present in about 1% w/w to about 15% w/w of the solids in the oral liquid formulation. In other embodiments, sodium citrate dihydrate is present in about 1% w/w, about 1.1% w/w, about 1.2% w/w, about 1.3% w/w, about 1.4% w/w, about 1.5% w/w, about 1.6% w/w, about 1.7% w/w, about 1.8% w/w, about 1.9% w/w, about 2% w/w, about 2.1% w/w, about 2.2% w/w, about 2.3% w/w, about 2.4% w/w, about 2.5% w/w, about 2.6% w/w, about 2.7% w/w, about 2.8% w/w, about 2.9% w/w, about 3% w/w, about 3.1% w/w, about 3.2% w/w, about 3.3% w/w, about 3.4% w/w, about 3.5% w/w, about 3.6% w/w, about 3.7% w/w, about 3.8% w/w, about 3.9% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 10.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 7.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 4.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 2.9% w/w of the solids in the oral liquid formulation.

In other embodiments, sodium citrate dihydrate is not added to the formulation.

Additional Excipients

In further embodiments, the enalapril liquid formulation described herein comprises additional excipients including, but not limited to, glidants, flavoring agents, coloring agents and thickeners. Additional excipients such as bulking agents, tonicity agents and chelating agents are within the scope of the embodiments.

Glidants are substances that improve flowability of a powder. Suitable glidants include, but are not limited to, calcium phosphate tribasic, calcium silicate, cellulose (powdered), colloidal silicon dioxide, magnesium silicate, magnesium trisilicate, silicon dioxide, starch, talc and the like. In some embodiments, the enalapril powder formulations described herein comprise a glidant. In some embodiments the glidant is not colloidal silicon dioxide.

In another embodiment, the enalapril liquid formulation comprises a flavoring agent or flavorant to enhance the taste or aroma of the formulation in liquid form. Suitable natural or synthetic flavoring agents can be selected from standard reference books, for example Fenaroli's Handbook of Flavor Ingredients, 3rd edition (1995). Non-limiting examples of suitable natural flavors, some of which can readily be simulated with synthetic agents or combinations thereof, include almond, anise, apple, apricot, bergamot, blackberry, blackcurrant, blueberry, cacao, caramel, cherry, cinnamon, clove, coffee, coriander, cranberry, cumin, dill, eucalyptus, fennel, fig, ginger, grape, grapefruit, guava, hop, lemon, licorice, lime, malt, mandarin, molasses, nutmeg, mixed berry, orange, peach, pear, peppermint, pineapple, raspberry, rose, spearmint, strawberry, tangerine, tea, vanilla, wintergreen, etc. Also useful, particularly where the formulation is intended primarily for pediatric use, is tutti-frutti or bubblegum flavor, a compounded flavoring agent based on fruit flavors. Presently preferred flavoring agents include anise, cinnamon, cacao, orange, peppermint, cherry (in particular wild cherry), grape, bubblegum, vanilla, and mixed berry. In some embodiments, the enalapril liquid formulation described herein comprises a mixed berry flavoring agent. Flavoring agents can be used singly or in combinations of two or more.

In further embodiments, the enalapril liquid formulation comprises a coloring agent for identity and/or aesthetic purposes. Suitable coloring agents illustratively include FD&C Red No. 3, FD&C Red No. 20, FD&C Red No. 40, FD&C Yellow No. 6, FD&C Blue No. 2, FD&C Green No. 5, FD&C Orange No. 5, caramel, ferric oxide and mixtures thereof.

Thickeners impart viscosity or weight to the resultant liquid forms from the enalapril formulation described herein. Exemplary thickeners include dextrin, cellulose derivatives (carboxymethylcellulose and its salts, ethylcellulose, hydroxyethyl cellulose, methylcellulose, hypromellose, and the like) starches, pectin, polyethylene glycol, polyethylene oxide, trehalose and certain gums (xanthan gum, locust bean gum, etc.). In certain embodiments, the enalapril liquid formulation comprises a thickener.

Additional excipients are contemplated in the enalapril liquid formulation embodiments. These additional excipients are selected based on function and compatibility with the enalapril liquid formulations described herein and may be found, for example in *Remington: The Science and Practice of Pharmacy*. Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*. (Easton, Pa.: Mack Publishing Co 1975); Liberman, H. A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms* (New York, N.Y.: Marcel Decker 1980); and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed (Lippincott Williams & Wilkins 1999), herein incorporated by reference in their entirety.

Stability

The main enalapril degradants are enalapril diketopiperazine and enalaprilat.

The enalapril oral liquid formulations described herein are stable in various storage conditions including refrigerated, ambient and accelerated conditions. Stable as used herein refers to enalapril oral liquid formulations having about 95% or greater of the initial enalapril amount and about 5% w/w or less total impurities or related substances at the end of a given storage period. The percentage of impurities is calculated from the amount of impurities relative to the amount of enalapril. Stability is assessed by HPLC or any other known testing method. In some embodiments, the stable enalapril oral liquid formulations have about 5% w/w, about 4% w/w, about 3% w/w, about 2.5% w/w, about 2% w/w, about 1.5% w/w, about 1% w/w, or about 0.5% w/w total impurities or related substances. In other embodiments, the stable enalapril oral liquid formulations have about 5% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 4%

w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 3% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 2% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 1% w/w total impurities or related substances.

At refrigerated condition, the enalapril oral liquid formulations described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 6 months, at least 9 months, at least 12 months, at least 15 months, at least 18 months, at least 24 months, at least 30 months and at least 36 months. In some embodiments, refrigerated condition is 5±3° C. In some embodiments, refrigerated condition is about 2° C., about 2.1° C., about 2.2° C., about 2.3° C., about 2.4° C., about 2.5° C., about 2.6° C., about 2.7° C., about 2.8° C., about 2.9° C., about 3° C., about 3.1° C., about 3.2° C., about 3.3° C., about 3.4° C., about 3.5° C., about 3.6° C., about 3.7° C., about 3.8° C., about 3.9° C., about 4° C., about 4.1° C., about 4.2° C., about 4.3° C., about 4.4° C., about 4.5° C., about 4.6° C., about 4.7° C., about 4.8° C., about 4.9° C., about 5° C., about 5.1° C., about 5.2° C., about 5.3° C., about 5.4° C., about 5.5° C., about 5.6° C., about 5.7° C., about 5.8° C., about 5.9° C., about 6° C., about 6.1° C., about 6.2° C., about 6.3° C., about 6.4° C., about 6.5° C., about 6.6° C., about 6.7° C., about 6.8° C., about 6.9° C., about 7° C., about 7.1° C., about 7.2° C., about 7.3° C., about 7.4° C., about 7.5° C., about 7.6° C., about 7.7° C., about 7.8° C., about 7.9° C., or about 8° C. At accelerated conditions, the enalapril oral liquid formulations described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months or at least 12 months. Accelerated conditions for the enalapril oral liquid formulations described herein include temperature and/or relative humidity (RH) that are at or above ambient levels (e.g. 25±5° C.; 55±10% RH). In some instances, an accelerated condition is at about 25° C., about 30° C., about 35° C., about 40° C., about 45° C., about 50° C., about 55° C. or about 60° C. In other instances, an accelerated condition is above 55% RH, about 65% RH, about 70% RH, about 75% RH or about 80% RH. In further instances, an accelerated condition is about 40° C. or 60° C. at ambient humidity. In yet further instances, an accelerated condition is about 40° C. at 75±5% RH humidity.

Enalapril Oral Powder Formulation

In another aspect, enalapril oral liquid formulations described herein are prepared from the reconstitution of an enalapril powder formulation. In some embodiments, the enalapril powder formulation comprising enalapril, a sweetener, a preservative, and optionally an excipient is dissolved in water, a buffer, other aqueous solvent, or a liquid to form an enalapril oral liquid formulation. In one embodiment, the sweetening agent is sucralose. In one embodiment, the sweetener is not mannitol. In one embodiment, the sweetening agent is xylitol. In another embodiment, the preservative is sodium benzoate. In one embodiment, the preservative is a paraben preservative. In one aspect, the enalapril powder formulation described herein comprises enalapril, sucralose, and sodium benzoate. In some embodiments, the enalapril powder formulation herein further comprises a flavoring agent. In some embodiments, the enalapril powder formulation herein further comprises one or more buffering agents.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w to about 30% w/w of the powder formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w, about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about 15.5% w/w, about 16% w/w, about 16.5% w/w, about 17% w/w, about 17.5% w/w, about 18% w/w, about 18.5% w/w, about 19% w/w, about 19.5% w/w, about 20% w/w, about 20.5% w/w, about 21% w/w, about 21.5% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5% w/w, about 25% w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the powder formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 10% w/w to about 25% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 13.5% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 19.5% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 24.5% w/w of the powder formulation. In some embodiments, enalapril is present in about 10.5% w/w of the powder formulation. In some embodiments, enalapril is present in about 14.5% w/w of the powder formulation. In some embodiments, enalapril is present in about 18% w/w of the powder formulation.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w to about 1% w/w of the powder formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w, about 0.15% w/w, about 0.2% w/w, about 0.25% w/w, about 0.3% w/w, about 0.35% w/w, about 0.4% w/w, about 0.45% w/w, about 0.5% w/w, about 0.55% w/w, about 0.6% w/w, about 0.65% w/w, about 0.7% w/w, about 0.75% w/w, about 0.8% w/w, about 0.85% w/w, about 0.9% w/w, about 0.95% w/w, or about 1% w/w of the powder formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.4% w/w to about 0.7% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 0.45% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 0.6% w/w of the powder formulation. In some embodiments, enalapril is present in about 0.4% w/w of the powder formulation. In some embodiments, enalapril is present in about 0.5% w/w of the powder formulation.

Various amounts and concentrations of other components (sweeteners, buffers, preservatives, and the like) in the enalapril powder formulations are found in the previous section describing the amounts and concentrations for the analogous enalapril oral liquid formulations. For example, in some embodiments where sucralose is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation; in an analogous enalapril powder formulation, sucralose would be about 1% w/w to about 30% w/w in the powder formulation. In some embodiments where sodium benzoate is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation, in an analogous

enalapril powder formulation sodium benzoate is present in about 1% w/w to about 30% w/w in the powder formulation.

Liquid vehicles suitable for the enalapril powder formulations to be reconstituted into an oral solution described herein are selected for a particular oral liquid formulation (solution, suspension, etc.) as well as other qualities such as clarity, toxicity, viscosity, compatibility with excipients, chemical inertness, palatability, odor, color and economy. Exemplary liquid vehicles include water, ethyl alcohol, glycerin, propylene glycol, syrup (sugar or other sweetener based, e.g., Ora-Sweet® SF sugar-free flavored syrup), juices (apple, grape, orange, cranberry, cherry, tomato and the like), other beverages (tea, coffee, soft drinks, milk and the like), oils (olive, soybean, corn, mineral, castor and the like), and combinations or mixtures thereof. Certain liquid vehicles, e.g., oil and water, can be combined together to form emulsions. In some embodiments, water is used for as a vehicle for a enalapril oral liquid formulation. In other embodiments, a syrup is used for as a vehicle for a enalapril oral liquid formulation. In yet other embodiments, a juice is used for as a vehicle for a enalapril oral liquid formulation.

Buffering agents maintain the pH of the liquid enalapril formulation. Non-limiting examples of buffering agents include, but are not limited to sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium gluconate, aluminum hydroxide, aluminum hydroxide/sodium bicarbonate co precipitate, mixture of an amino acid and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer. Additional buffering agents include citric acid, sodium citrate, sodium tartrate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, sodium acetate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, and other calcium salts. Some buffering agents also impart effervescent qualities when a powder is reconstituted in a solution.

In some embodiments, the reconstituted oral liquid formulation comprises a buffer. In some embodiments, the buffer comprises citric acid and sodium citrate.

In further embodiments, the enalapril powder formulation described herein comprises additional excipients including, but not limited to, glidants, flavoring agents, coloring agents and thickeners. Additional excipients such as bulking agents, tonicity agents and chelating agents are within the scope of the embodiments.

Glidants are substances that improve flowability of a powder. Suitable glidants include, but are not limited to, calcium phosphate tribasic, calcium silicate, cellulose (powdered), colloidal silicon dioxide, magnesium silicate, magnesium trisilicate, silicon dioxide, starch, talc and the like. In some embodiments, the enalapril powder formulations described herein comprise a glidant.

In another embodiment, the enalapril powder formulation described herein comprises a flavoring agent or flavorant to enhance the taste or aroma of the formulation in liquid form. Suitable natural or synthetic flavoring agents can be selected from standard reference books, for example Fenaroli's Handbook of Flavor Ingredients, 3rd edition (1995). Non-limiting examples of suitable natural flavors, some of which can readily be simulated with synthetic agents or combinations thereof, include almond, anise, apple, apricot, bergamot, blackberry, blackcurrant, blueberry, cacao, caramel, cherry, cinnamon, clove, coffee, coriander, cranberry, cumin, dill, eucalyptus, fennel, fig, ginger, grape, grapefruit, guava, hop, lemon, licorice, lime, malt, mandarin, molasses, nutmeg, mixed berry, orange, peach, pear, peppermint, pineapple, raspberry, rose, spearmint, strawberry, tangerine, tea, vanilla, wintergreen, etc. Also useful, particularly where the formulation is intended primarily for pediatric use, is tutti-frutti or bubblegum flavor, a compounded flavoring agent based on fruit flavors. Presently preferred flavoring agents include anise, cinnamon, cacao, orange, peppermint, cherry (in particular wild cherry), grape, bubblegum, vanilla, and mixed berry. Flavoring agents can be used singly or in combinations of two or more.

In further embodiments, the enalapril powder formulation described herein comprises a coloring agent for identity and/or aesthetic purposes. Suitable coloring agents illustratively include FD&C Red No. 3, FD&C Red No. 20, FD&C Red No. 40, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, caramel, ferric oxide and mixtures thereof.

In further embodiments, the enalapril powder formulation described herein comprises a thickener. Thickeners impart viscosity or weight to the resultant liquid forms from the enalapril formulation described herein. Exemplary thickeners include dextrin, cellulose derivatives (carboxymethylcellulose and its salts, ethylcellulose, hydroxyethyl cellulose, methylcellulose, hypromellose, and the like) starches, pectin, polyethylene glycol, polyethylene oxide, trehalose and certain gums (xanthan gum, locust bean gum, etc.).

Additional excipients are contemplated in the enalapril powder formulation embodiments. These additional excipients are selected based on function and compatibility with the the enalapril powder formulation described herein and may be found, for example in *Remington: The Science and Practice of Pharmacy*. Nineteeth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*. (Easton, Pa.: Mack Publishing Co 1975); Liberman, H. A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms* (New York, N.Y.: Marcel Decker 1980); and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed (Lippincott Williams & Wilkins 1999), herein incorporated by reference in their entirety.

In some embodiments, the enalapril oral liquid formulation prepared from the powder formulations described herein are homogenous. Homogenous liquids as used herein refer to those liquids that are uniform in appearance, identity, consistency and drug concentration per volume. Non-homogenous liquids include such liquids that have varied coloring, viscosity and/or aggregation of solid particulates, as well as non-uniform drug concentration in a given unit volume. Homogeneity in liquids are assessed by qualitative identification or appearance tests and/or quantitative HPLC testing or the like. The mixing methods and excipients described herein are selected to impart a homogenous quality to a resultant enalapril oral liquid formulation.

Mixing methods encompass any type of mixing that result in a homogenous enalapril oral liquid formulation. In some embodiments, a quantity of an enalapril powder formulation is added to a liquid vehicle and then mixed by a stirring, shaking, swirling, agitation element or a combination thereof. In certain instances, a fraction of a enalapril powder formulation (i.e., one-half, one-third, one-fourth, etc.) is added to a liquid vehicle, mixed by stirring, shaking, swirling, agitation or a combination thereof, and the subsequent powder fraction(s) is added and mixed. In other embodi-

ments, a liquid vehicle is added to an enalapril powder formulation in a container, for example, a bottle, vial, bag, beaker, syringe, or the like. The container is then mixed by stirring, shaking, swirling, agitation, inversion or a combination thereof. In certain instances, a fractional volume of the liquid vehicle (i.e., one-half, one-third, one-fourth volume, etc.) is added to a enalapril powder formulation in a container, mixed by stirring, shaking, swirling, agitation, inversion or a combination thereof; and the subsequent liquid fraction(s) is added and mixed. In certain instances, a one-half fractional volume of the liquid vehicle is added to an enalapril powder formulation in a container and mixing by shaking; the other one-half fractional volume of the liquid vehicle is then subsequently added and mixed. In any of the above embodiments, mixing (i.e., stirring, shaking, swirling, agitation, inversion or a combination thereof) occurs for a certain time intervals such as about 10 seconds, about 20 seconds, about 30 seconds, about 45 seconds, about 60 seconds, about 90 seconds, about 120 seconds, about 2.5 minutes, about 3 minutes, about 3.5 minutes, about 4 minutes, or about 5 minutes. In embodiments, where there are two or more mixing steps, the time intervals for each mixing can be the same (e.g., 2×10 seconds) or different (e.g., 10 seconds for first mixing and 20 seconds for second mixing). In any of the above embodiments, a enalapril oral liquid formulation is allowed to stand for a period of time such as about 10 minutes, about 20 minutes, about 30 minutes, about 45 minutes, about 1 hour, about 1.5 hours or about 2 hours, to allow any air bubbles resultant from any of the mixing methods to dissipate.

Stability of Enalapril Powder Formulation

The enalapril powder formulations described herein are stable in various storage conditions including refrigerated, ambient and accelerated conditions. Stable as used herein refer to enalapril powder formulations having about 95% or greater of the initial enalapril amount and 5% w/w or less total impurities or related substances at the end of a given storage period. The percentage of impurities is calculated from the amount of impurities relative to the amount of enalapril. Stability is assessed by HPLC or any other known testing method. In some embodiments, the stable enalapril powder formulations have about 5% w/w, about 4% w/w, about 3% w/w, about 2.5% w/w, about 2% w/w, about 1.5% w/w, about 1% w/w, or about 0.5% w/w total impurities or related substances. In other embodiments, the stable enalapril powder formulations have about 5% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 4% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 3% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 2% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 1% w/w total impurities or related substances.

At refrigerated and ambient conditions, in some embodiments, the enalapril powder formulations described herein are stable for at least 1 week, 2 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 12 weeks, 16 weeks, 20 weeks, at least 24 weeks, at least 30 weeks, or at least 36 weeks. At accelerated conditions, in some embodiments, the enalapril powder formulations described herein are stable for at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks or at least 12 weeks. Accelerated conditions for the enalapril powder formulations described herein include temperature and/or relative humidity (RH) that are above ambient levels (e.g. 25±4° C.; 55±10% RH). In some instances, an accelerated condition is at about 30° C., about 35° C., about 40° C., about 45° C., about 50° C., about 55° C. or about 60° C. In other instances, an accelerated condition is above 65% RH, about 70% RH, about 75% RH or about 80% RH. In further instances, an accelerated condition is about 40° C. or 60° C. at ambient humidity. In yet further instances, an accelerated condition is about 40° C. at 75±5% RH humidity.

Kits and Articles of Manufacture

For the enalapril powder and liquid formulations described herein, kits and articles of manufacture are also described. Such kits can comprise a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method described herein including an enalapril powder or liquid formulation. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers can be formed from a variety of materials such as glass or plastic.

A kit will typically may comprise one or more additional containers, each with one or more of various materials (such as reagents, optionally in concentrated form, and/or devices) desirable from a commercial and user standpoint for an enalapril powder or liquid formulation described herein. Non-limiting examples of such materials include, but not limited to, buffers, diluents, filters, needles, syringes; carrier, package, container, vial and/or tube labels listing contents and/or instructions for use, and package inserts with instructions for use associated with an enalapril powder or liquid formulation. A set of instructions will also typically be included.

A label can be on or associated with the container. A label can be on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label can be associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. A label can be used to indicate that the contents are to be used for a specific therapeutic application. The label can also indicate directions for use of the contents, such as in the methods described herein.

Methods

Provided herein, in one aspect, are methods of treatment comprising administration of the enalapril oral liquid formulations described herein to a subject. In some embodiments, the enalapril oral liquid formulations described herein treat hypertension in a subject. Hypertension as used herein includes both primary (essential) hypertension and secondary hypertension. In certain instances, hypertension is classified in cases when blood pressure values are greater than or equal to 140/90 (systolic/diastolic) mm Hg in a subject. In certain instances, the enalapril oral liquid formulations described herein treat a subject having a blood pressure values are greater than or equal to 140/90 mm Hg. In certain instances, the enalapril oral liquid formulations described herein treat primary (essential) hypertension in a subject. In other instances, the enalapril oral liquid formulations described herein treat secondary hypertension in a subject.

In other embodiments, the enalapril oral liquid formulations described herein treat prehypertension in a subject. Prehypertension as used herein refers to cases where a subject's blood pressure is elevated above normal but not to

the level considered to be hypertension. In some instances, prehypertension is classified in cases when blood pressure values are 120-139/80-89 mm Hg. In certain instances, the enalapril oral liquid formulations described herein treat a subject having blood pressure values of 120-139/80-89 mm Hg.

In yet other embodiments, the enalapril oral liquid formulations described herein are prophylactically administered to subjects suspected of having, predisposed to, or at risk of developing hypertension. In some embodiments, the administration of enalapril oral liquid formulations described herein allow for early intervention prior to onset of hypertension. In certain embodiments, upon detection of a biomarker, environmental, genetic factor, or other marker, the enalapril oral liquid formulations described herein are prophylactically administered to subjects.

In further embodiments, the enalapril oral liquid formulations described herein treat heart failure (e.g., symptomatic congestive), asymptomatic left ventricular dysfunction, myocardial infarction, diabetic nephropathy and chronic renal failure. In certain instances, the enalapril oral liquid formulations described herein treat symptomatic congestive heart failure. In other instances, the enalapril oral liquid formulations described herein treat asymptomatic left ventricular dysfunction. In further instances, the enalapril oral liquid formulations described herein treat myocardial infarction. In yet further instances, the enalapril oral liquid formulations described herein treat diabetic nephropathy. In yet further instances, the enalapril oral liquid formulations described herein treat chronic renal failure.

Dosing

In one aspect, the enalapril oral liquid formulations are used for the treatment of diseases and conditions described herein. In addition, a method for treating any of the diseases or conditions described herein in a subject in need of such treatment, involves administration of enalapril oral liquid formulations in therapeutically effective amounts to said subject.

Dosages of enalapril oral liquid formulations described can be determined by any suitable method. Maximum tolerated doses (MTD) and maximum response doses (MRD) for enalapril and/or enalaprilat can be determined via established animal and human experimental protocols as well as in the examples described herein. For example, toxicity and therapeutic efficacy of enalapril and/or enalaprilat can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between the toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD_{50} and ED_{50}. Enalapril dosages exhibiting high therapeutic indices are of interest. The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED_{50} with minimal toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. Additional relative dosages, represented as a percent of maximal response or of maximum tolerated dose, are readily obtained via the protocols.

In some embodiments, the amount of a given enalapril oral liquid formulation that corresponds to such an amount varies depending upon factors such as the particular enalapril salt or form, disease condition and its severity, the identity (e.g., weight, sex) of the subject or host in need of treatment, but can nevertheless be determined according to the particular circumstances surrounding the case, including, e.g., the specific agent being administered, the liquid composition type, the condition being treated, and the subject or host being treated.

In some embodiments, the enalapril oral liquid formulations described herein are provided in a dose per day from about 0.01 mg to 100 mg, from about 0.1 mg to about 80 mg, from about 1 to about 60, from about 2 mg to about 40 mg of enalapril. In certain embodiments, the enalapril oral liquid formulations described herein are provided in a daily dose of about 0.01 mg, about 0.05 mg, about 0.1 mg, about 0.2 mg, about 0.4 mg, about 0.6 mg, about 0.8 mg, about 1 mg, about 1.5 mg, about 2 mg, about 2.5 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 76, mg, about 80 mg, about 85 mg, about 90 mg or about 100 mg, or any range derivable therein. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 1 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 2 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 3 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 4 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 5 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 6 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 7 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 8 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 9 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 10 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 11 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 12 mg. The dose per day described herein can be given once per day or multiple times per day in the form of sub-doses given b.i.d., t.i.d., q.i.d., or the like where the number of sub-doses equal the dose per day.

In further embodiments, the daily dosages appropriate for the enalapril oral liquid formulations described herein are from about 0.01 to about 1.0 mg/kg per body weight. In one embodiment, the daily dosages appropriate for the enalapril oral liquid formulations are from about 0.02 to about 0.8 mg/kg enalapril per body weight. In another embodiment, the daily dosage appropriate for the enalapril oral liquid formulations are from about 0.05 to about 0.6 mg/kg per body weight. In another embodiment, the daily dosage appropriate for the enalapril oral liquid formulations is about 0.05 mg/kg, about 0.06 mg/kg, about 0.07 mg/kg, about 0.08 mg/kg, about 0.10 mg/kg, about 0.15 mg/kg, about 0.20 mg/kg, about 0.25 mg/kg, about 0.30 mg/kg, about 0.40 mg/kg, about 0.50 mg/kg, or about 0.60 mg/kg.

In other embodiments the enalapril oral liquid formulations are provided at the maximum tolerated dose (MTD) for enalapril and/or enalaprilat. In other embodiments, the

amount of the enalapril oral liquid formulations administered is from about 10% to about 90% of the maximum tolerated dose (MTD), from about 25% to about 75% of the MTD, or about 50% of the MTD. In particular embodiments, the amount of the enalapril oral liquid formulations administered is from about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or higher, or any range derivable therein, of the MTD for enalapril and/or enalaprilat.

In further embodiments, the enalapril oral liquid formulations are provided in a dosage that is similar, comparable or equivalent to a dosage of a known enalapril tablet formulation. In other embodiments, the enalapril oral liquid formulations are provided in a dosage that provides a similar, comparable or equivalent pharmacokinetic parameters (e.g., AUC, C_{max}, T_{max}, C_{min}, $T_{1/2}$) as a dosage of a known enalapril tablet formulation. Similar, comparable or equivalent pharmacokinetic parameters, in some instances, refer to within 80% to 125%, 80% to 120%, 85% to 125%, 90% to 110%, or increments therein, of the given values. It should be recognized that the ranges can, but need not be symmetrical, e.g., 85% to 105%.

Administration

Administration of an enalapril oral liquid formulation is at a dosage described herein or at other dose levels and formulations determined and contemplated by a medical practitioner. In certain embodiments, the enalapril oral liquid formulations described herein are administered for prophylactic and/or therapeutic treatments. In certain therapeutic applications, the enalapril oral liquid formulations are administered to a patient already suffering from a disease, e.g., hypertension, in an amount sufficient to cure the disease or at least partially arrest or ameliorate the symptoms, e.g., lower blood pressure. Amounts effective for this use depend on the severity of the disease, previous therapy, the patient's health status, weight, and response to the enalapril formulations, and the judgment of the treating physician. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation clinical trial.

In prophylactic applications, the enalapril oral liquid formulations described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, e.g., hypertension. Such an amount is defined to be a "prophylactically effective amount or dose." In this use, the precise amounts also depend on the patient's state of health, weight, and the like. When used in a patient, effective amounts for this use will depend on the risk or susceptibility of developing the particular disease, previous therapy, the patient's health status and response to the enalapril formulations, and the judgment of the treating physician.

In certain embodiments wherein the patient's condition does not improve, upon the doctor's discretion the administration of an enalapril oral liquid formulations described herein are administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease. In other embodiments, administration of an enalapril oral liquid formulation continues until complete or partial response of a disease.

In certain embodiments wherein a patient's status does improve, the dose of an enalapril oral liquid formulation being administered may be temporarily reduced or temporarily suspended for a certain length of time (i.e., a "drug holiday"). In specific embodiments, the length of the drug holiday is between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, and 365 days. The dose reduction during a drug holiday is, by way of example only, by 10%-100%, including by way of example only 10%, 15%, 20%, 2^5%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 100%.

In some embodiments, enalapril oral liquid formulations described herein are administered chronically. For example, in some embodiments, an enalapril oral liquid formulation is administered as a continuous dose, i.e., administered daily to a subject. In some other embodiments, enalapril oral liquid formulations described herein are administered intermittently (e.g. drug holiday that includes a period of time in which the formulation is not administered or is administered in a reduced amount).

In some embodiments an enalapril oral liquid formulation is administered to a subject who is in a fasted state. A fasted state refers to a subject who has gone without food or fasted for a certain period of time. General fasting periods include at least 4 hours, at least 6 hours, at least 8 hours, at least 10 hours, at least 12 hours, at least 14 hours and at least 16 hours without food. In some embodiments, an enalapril oral liquid formulation is administered orally to a subject who is in a fasted state for at least 8 hours. In other embodiments, an enalapril oral liquid formulation is administered to a subject who is in a fasted state for at least 10 hours. In yet other embodiments, an enalapril oral liquid formulation is administered to a subject who is in a fasted state for at least 12 hours. In other embodiments, an enalapril oral liquid formulation is administered to a subject who has fasted overnight.

In other embodiments an enalapril oral liquid formulation is administered to a subject who is in a fed state. A fed state refers to a subject who has taken food or has had a meal. In certain embodiments, an enalapril oral liquid formulation is administered to a subject in a fed state 5 minutes post-meal, 10 minutes post-meal, 15 minutes post-meal, 20 minutes post-meal, 30 minutes post-meal, 40 minutes post-meal, 50 minutes post-meal, 1 hour post-meal, or 2 hours post-meal. In certain instances, an enalapril oral liquid formulation is administered to a subject in a fed state 30 minutes post-meal. In other instances, an enalapril oral liquid formulation is administered to a subject in a fed state 1 hour post-meal. In yet further embodiments, an enalapril oral liquid formulation is administered to a subject with food.

In further embodiments described herein, an enalapril oral liquid formulation is administered at a certain time of day for the entire administration period. For example, an enalapril oral liquid formulation can be administered at a certain time in the morning, in the evening, or prior to bed. In certain instances, an enalapril oral liquid formulation is administered in the morning. In other embodiments, an enalapril oral liquid formulation can be administered at different times of the day for the entire administration period. For example, an enalapril oral liquid formulation can be administered on 8:00 am in the morning for the first day, 12 pm noon for the next day or administration, 4 pm in the afternoon for the third day or administration, and so on.

Further Combinations

The treatment of certain diseases or conditions (e.g., hypertension, heart failure, myocardial infarction and the like) in a subject with an enalapril oral liquid formulation described herein encompass additional therapies and treatment regimens with other agents in some embodiments. Such additional therapies and treatment regimens can

include another therapy, e.g., additional anti-hypertensives, for treatment of the particular disease or condition in some embodiments. Alternatively, in other embodiments, additional therapies and treatment regimens include other agents used to treat adjunct conditions associated with the disease or condition or a side effect from the enalapril oral liquid formulation in the therapy.

Additional agents for use in combination with an enalapril oral liquid formulation described herein include, but are not limited to, diuretics (loop, thiazide, potassium-sparing, and the like), beta blockers (metoprolol, propanolol, pronethalol, and the like), alpha blockers (phentolamine, phenoxybenzamine, tamsulosin, prazosin, and the like), mixed alpha and beta blockers (bucindolol, carvedilol, labetalol), calcium channel blockers (dihydropyridines such as nifedipine, amlodipine, etc., dilitazem, verapamil and the like), angiotensin II receptor antagonists (saralasin, lsartan, eprosartin, irbesartan, valsartan, and the like), other ACE inhibitors (captopril, quinapril, ramipril, lisinopril, zofenopril, and the like), aldosterone antagonists (eplerenone, spironolactone and the like), vasodilators (hydralazine and the like) and alpha-2 agonists (clonidine, moxonidine, guanabenz and the like).

Certain Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments described herein, certain preferred methods, devices, and materials are now described.

As used herein and in the appended claims, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to "an excipient" is a reference to one or more excipients and equivalents thereof known to those skilled in the art, and so forth.

The term "about" is used to indicate that a value includes the standard level of error for the device or method being employed to determine the value. The use of the term "or" in the claims is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and to "and/or." The terms "comprise," "have" and "include" are open-ended linking verbs. Any forms or tenses of one or more of these verbs, such as "comprises," "comprising," "has," "having," "includes" and "including," are also open-ended. For example, any method that "comprises," "has" or "includes" one or more steps is not limited to possessing only those one or more steps and also covers other unlisted steps.

"Optional" or "optionally" may be taken to mean that the subsequently described structure, event or circumstance may or may not occur, and that the description includes instances where the events occurs and instances where it does not.

As used herein, the term "therapeutic" means an agent utilized to treat, combat, ameliorate, prevent or improve an unwanted condition or disease of a patient. In some embodiments, a therapeutic agent such as enalapril is directed to the treatment and/or the amelioration of, reversal of, or stabilization of the symptoms of hypertension described herein.

"Administering" when used in conjunction with a therapeutic means to administer a therapeutic systemically or locally, as directly into or onto a target tissue, or to administer a therapeutic to a patient whereby the therapeutic positively impacts the tissue to which it is targeted. Thus, as used herein, the term "administering", when used in conjunction with an enalapril formulation, can include, but is not limited to, providing an enalapril formulation into or onto the target tissue; providing an enalapril formulation systemically to a patient by, e.g., oral administration whereby the therapeutic reaches the target tissue or cells. "Administering" a formulation may be accomplished by injection, topical administration, and oral administration or by other methods alone or in combination with other known techniques.

The term "animal" as used herein includes, but is not limited to, humans and non-human vertebrates such as wild, domestic and farm animals. As used herein, the terms "patient," "subject" and "individual" are intended to include living organisms in which certain conditions as described herein can occur. Examples include humans, monkeys, cows, sheep, goats, dogs, cats, mice, rats, and transgenic species thereof. In a preferred embodiment, the patient is a primate. In certain embodiments, the primate or subject is a human. In certain instances, the human is an adult. In certain instances, the human is child. In further instances, the human is 12 years of age or younger. In certain instances, the human is elderly. In other instances, the human is 60 years of age or older. Other examples of subjects include experimental animals such as mice, rats, dogs, cats, goats, sheep, pigs, and cows. The experimental animal can be an animal model for a disorder, e.g., a transgenic mouse with hypertensive pathology. A patient can be a human suffering from hypertension, or its variants or etiological forms.

By "pharmaceutically acceptable", it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The term "pharmaceutical composition" shall mean a composition comprising at least one active ingredient, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

A "therapeutically effective amount" or "effective amount" as used herein refers to the amount of active compound or pharmaceutical agent that elicits a biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following: (1) preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease, (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology), and (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology). As such, a non-limiting example of a "therapeutically effective amount" or "effective amount" of a formulation of the present disclosure may be used to inhibit, block,

or reverse the activation, migration, or proliferation of cells or to effectively treat hypertension or ameliorate the symptoms of hypertension.

The terms "treat," "treated," "treatment," or "treating" as used herein refers to both therapeutic treatment in some embodiments and prophylactic or preventative measures in other embodiments, wherein the object is to prevent or slow (lessen) an undesired physiological condition, disorder or disease, or to obtain beneficial or desired clinical results. For the purposes described herein, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of the condition, disorder or disease; stabilization (i.e., not worsening) of the state of the condition, disorder or disease; delay in onset or slowing of the progression of the condition, disorder or disease; amelioration of the condition, disorder or disease state; and remission (whether partial or total), whether detectable or undetectable, or enhancement or improvement of the condition, disorder or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment. A prophylactic benefit of treatment includes prevention of a condition, retarding the progress of a condition, stabilization of a condition, or decreasing the likelihood of occurrence of a condition. As used herein, "treat," "treated," "treatment," or "treating" includes prophylaxis in some embodiments.

EXAMPLES

Example A: Effect of pH on the Formation of Degradants in Enalapril Formulations at 60° C.

Formulations were prepared containing enalapril maleate according to Table A-1. The pH of each solution was recorded. Five milliliters of each formulation were transferred to each of four 3-dram glass screw-capped vials with Teflon inserts in the caps. The vials were placed into a 60° C. heating chamber then one vial removed and analyzed by HPLC at times of zero, ~97 and ~180 hours.

TABLE A-1

Formulation (in mg/mL) of Enalapril Formulations at Varying pH and Citrate Buffer Concentration

	Formulation (mM citrate)					
Component	A1 (50)	A2 (50)	A3 (50)	A4 (50)	A5 (50)	A6 (25)
Enalapril maleate	1.0	1.0	1.0	1.0	1.0	1.0
Mannitol	50	50	50		50	6.0
Xylitol				50		
Citric acid, anhydrous	7.35	5.05	2.55	5.05	5.05	2.76
Sodium citrate, dihydrate	3.45	7.0	10.8	7.0	7.0	3.15
Sodium benzoate	1	1	1	1	1	
Methylparaben sodium					1.75	0.335
Propylparaben sodium						0.095
Potassium sorbate						1
Sucralose	0.75	0.75	0.75	0.75	0.75	0.75
Silicon dioxide						0.075
Mixed berry flavor (powdered)	0.5	0.5	0.5	0.5	0.5	0.5
Water	qs	qs	qs	qs	qs	qs
pH	3.4	4.4	5.2	4.4	4.5	4.4

qs = sufficient quantity

The results of the HPLC analysis for the two main degradants in the samples, enalapril diketopiperazine and enalaprilat, are provided in Table A-2.

TABLE A-2

Primary Degradants Present in the Formulations (% w/w of enalapril maleate)

Hours at 60° C.	Formulation A1	A2	A3	A4	A5	A6
Enalapril Diketopiperazine						
0	0.04	0.03	0.03	0.03	0.03	0.03
97	3.10	0.88	0.33	0.86	0.70	0.53
180	6.21	1.77	0.75	1.73	1.43	1.07
Enalaprilat						
0	0.09	0.15	0.29	0.14	0.16	0.12
97	5.20	16.9	47.4	16.1	20.3	15.6
180	9.94	34.8	113	33.5	42.2	31.7

Example B: Effect of Buffer Concentration on the Formation of Degradants in Enalapril Formulations at 60° C.

Formulations were prepared containing enalapril maleate according to Table B-1. The pH of each solution was measured and adjusted as needed to pH 3.3 with ~1N HCl or ~0.5N NaOH. Five milliliters of each formulation were transferred to each of six 3-dram glass screw-capped vials with Teflon inserts in the caps. The vials were placed into a 60° C. heating chamber then two vials were removed and analyzed by HPLC at times of zero, ~66 and ~139 hours.

TABLE B-1

Formulation (in mg/mL) of Enalapril Maleate Formulations at Varying Citrate Buffer Concentrations

	Formulation		
Component	B1 (5 mM citrate)	B2 (10 mM citrate)	B3 (20 mM citrate)
Enalapril maleate	1.0	1.0	1.0
Citric acid, anhydrous	0.82	1.65	3.29
Sodium citrate, anhydrous	0.19	0.38	0.75
Sodium benzoate	1.0	1.0	1.0
Sucralose	0.7	0.7	0.7
Mixed berry flavor (powdered)	0.5	0.5	0.5
Water	qs	qs	qs
pH	3.3	3.3	3.3

qs = sufficient quantity

The results of the HPLC analysis for the two main degradants in the samples, enalapril diketopiperazine and enalaprilat, are provided in Table B-2.

TABLE B-2

Primary Degradants Present in the Formulations (% w/w of enalapril maleate)

	Formulation		
Hours at 60° C.	B1 (5 mM citrate)	B2 (10 mM citrate)	B3 (20 mM citrate)
Enalapril Diketopiperazine			
0	0.01	0.01	0.01
66	1.57	1.63	1.79
139	3.70	3.94	4.24

TABLE B-2-continued

Primary Degradants Present in the Formulations (% w/w of enalapril maleate)			
	Formulation		
Hours at 60° C.	B1 (5 mM citrate)	B2 (10 mM citrate)	B3 (20 mM citrate)
Enalaprilat			
0	0.00	0.00	0.00
66	2.98	2.88	3.19
139	5.28	5.23	5.69

Example C: Stability of Enalapril Maleate Formulations Containing Paraben Preservatives

Powder formulations were prepared according to Table C-1. All components in each formulation except mannitol or xylitol were added to a 2.5 liter polypropylene screw capped bottle. The bottle was mixed by inversion in a Turbula® mixer for 5 minutes. The mannitol or xylitol was then added and the components mixed for 5 minutes, then the other half of the mannitol or xylitol was added and a final mix of 5 minutes was completed.

One liter of solution formulation was prepared for each formulation by adding an appropriate amount of each powdered formulation to a 1 liter volumetric flask and adding about 500 mL water. The powder was dissolved with mixing then the contents of the flask were brought to 1 liter with additional water. The amount of powder to add was determined such that the final concentration of enalapril maleate was 1.0 mg/mL. Fifty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5° C. 3° C., at room temperature (19-23° C.) and at 40° C. 2° C. At various times, bottles were removed from the storage condition and analyzed.

TABLE C-1

Composition of Enalapril Maleate Formulations					
Component	C1	C2	C3	C4	C5
Powder Formulation (grams)					
Enalapril maleate	12.3	12.3	8.86	2.16	2.16
Mannitol	74.4	74.4	394.0		
Xylitol				96.6	93.7
Citric acid, anhydrous	28.6	35.6	28.4	5.40	5.40
Sodium citrate, anhydrous	24.5	14.7	7.73	4.10	4.10
Sodium methylparaben	4.17	4.17	8.86	2.16	2.16
Sodium propylparaben	1.10	1.10			
Potassium sorbate	12.3	12.3			
Sodium benzoate			8.86	2.16	2.16
Xanthan Gum					1.62
Colloidal silicon dioxide	0.859	0.859	4.43		1.08
Sucralose	9.20	9.20	6.64	1.62	1.62
Mixed berry flavor	6.13	6.13	4.43	1.08	1.08
Total solids	173.5	170.7	472.3	115.2	115.2
Liquid Formulations (mg/mL)					
Enalapril maleate	1.00	1.00	1.00	1.00	1.00
Mannitol	6.07	6.07	44.5		
Xylitol				44.7	43.4
Citric acid, anhydrous	2.33	2.90	3.21	2.50	2.50
Sodium citrate, anhydrous	2.00	1.20	0.87	1.90	1.90

TABLE C-1-continued

Composition of Enalapril Maleate Formulations					
Component	C1	C2	C3	C4	C5
Sodium methylparaben	0.34	0.34	1.00	1.00	1.00
Sodium propylparaben	0.09	0.09	1.00		
Potassium sorbate	1.00	1.00			
Sodium benzoate			1.00	1.00	1.00
Xanthan Gum					0.75
Colloidal silicon dioxide	0.07	0.07	0.50		0.50
Sucralose	0.75	0.75	0.75	0.75	0.75
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50
pH (measured)	4.4	3.8	3.7	4.4	4.6

The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table C-2.

TABLE C-2

Degradant Content After Storage (% w/w of enalapril maleate)							
	Storage		Formulation				
	° C.	Weeks	C1	C2	C3	C4	C5
Liquid Formulations							
Diketopiperazine	5	0	0.03	0.04	0.04	0.02	0.02
		4	0.02	0.03	0.03	0.03	0.02
		8	0.03	0.04	0.04		
	19-23	0	0.03	0.04	0.04	0.02	0.02
		4	0.05	0.09	0.11	0.05	0.04
		8	0.08	0.17	0.19		
	40	0	0.03	0.04	0.04	0.02	0.02
		4	0.35	0.91	1.10	0.31	0.21
		8	0.65	1.80	2.05		
Enalaprilat	5	0	0.18	0.14	0.12	0.13	0.19
		4	0.18	0.15	0.12	0.43	0.53
		8	0.55	0.38	0.34		
	19-23	0	0.18	0.14	0.12	0.13	0.19
		4	1.35	0.83	0.80	1.75	2.29
		8	3.34	2.06	1.98		
	40	0	0.18	0.14	0.12	0.13	0.19
		4	10.49	6.08	6.11	12.30	16.14
		8	24.37	14.12	14.22		

Example D: Stability of Enalapril Maleate Formulations Containing Benzoate Preservative

Powder formulations were prepared according to Table D-1. All components in each formulation except enalapril maleate and mannitol or xylitol were blended with a mortar and pestle. The enalapril maleate was then triturated with the blend. The xylitol or mannitol was then triturated into the blend using a geometric dilution technique.

One liter of solution formulation was prepared for each formulation by adding an appropriate amount of each powdered formulation to a 1 liter volumetric flask and adding about 500 mL water. The powder was dissolved with mixing then the contents of the flask were brought to 1 liter with additional water. The amount of powder to add was determined such that the final concentration of enalapril maleate was 1.0 mg/mL. Fifty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5° C. 3° C., at room temperature (19-23° C.) and at 40° C. 2° C. At various times, bottles were removed from the storage condition and analyzed.

TABLE D-1

Composition of Enalapril Maleate Formulations

Component	D1	D2	D3	D4	D5	D6
Powder Formulation (grams)						
Enalapril maleate	3.63	3.63	3.63	3.63	8.86	2.16
Xylitol	537.2	176.1		537.2		
Mannitol			319.4		401.2	98.9
Citric acid, anhydrous	11.9	11.9	11.9	10.4	26.6	6.48
Sodium citrate, anhydrous	2.72	2.72	2.72	4.86	11.3	2.76
Sodium benzoate	3.63	3.63	3.63	3.63	8.86	2.16
Rebalance X60 (sucralose and maltodextrin)		10.9				
Sucralose					6.64	1.62
Saccharin sodium			7.26			
Colloidal silicon dioxide					4.43	
Mixed berry flavor	1.82	1.82	1.82	1.82	4.43	1.08
Total solids	561	211	350.	561	472.3	115.2
Liquid Formulations (mg/mL)						
Enalapril maleate	1.00	1.00	1.00	1.00	1.00	1.00
Xylitol	148.0	48.5		148.0		
Mannitol			88.0		45.3	45.8
Citric acid, anhydrous	3.29	3.29	3.29	2.85	3.00	3.00
Sodium citrate, anhydrous	0.75	0.75	0.75	1.34	1.28	1.28
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00
Rebalance X60 (sucralose and maltodextrin)		3.00				
Sucralose					0.75	0.75
Saccharin sodium			2.00			
Colloidal silicon dioxide					0.50	
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50	0.50
pH (measured)	3.2	3.2	3.4	3.7	3.6	3.6

The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table D-2.

TABLE D-2

Degradant Content After Storage (% w/w of enalapril maleate)

	Storage		Formulation					
	° C.	Weeks	D1	D2	D3	D4	D5	D6
Liquid Formulations								
Diketopi-perazine	5	0	0.04	0.02	0.03	0.03	0.04	0.04
		4	0.07	0.03	0.05	0.05	0.03	
		8	0.11	0.06	0.08	0.08	0.05	
		12	0.08	0.04	0.06	0.06		
		26	0.11	0.07	0.09	0.07		
	19-23	0	0.04	0.02	0.03	0.03	0.04	0.04
		4	0.27	0.21	0.24	0.16	0.12	0.12
		8	0.50	0.41	0.47	0.30	0.21	0.22
		12	0.62	0.52	0.58	0.35		
		26	1.39	1.20	1.33	0.76		
	40	0	0.04	0.02	0.03	0.03	0.04	0.04
		4	2.87	2.32	2.73	1.57	1.21	1.13
		8	5.13	4.42	5.44	2.97	2.23	2.16
		12	6.86	5.90	6.90	3.91		
		26	13.63	12.18	13.56	7.74		
Enalaprilat	5	0	0.03	0.02	0.03	0.03	0.13	0.14
		4	0.15	0.12	0.06	0.17	0.13	
		8	0.22	0.19	0.22	0.27	0.34	
		12	0.20	0.17	0.19	0.22		
		8	0.32	0.30	0.30	0.39		
	19-23	0	0.03	0.02	0.03	0.03	0.13	0.14
		4	0.69	0.66	0.69	0.86	0.74	0.76
		8	1.38	1.33	1.41	1.68	1.83	1.82
		12	1.71	1.68	1.73	2.15		
		26	3.63	3.61	3.59	4.55		
	40	0	0.03	0.02	0.03	0.03	0.13	0.14
		4	4.76	4.42	4.76	6.45	5.55	5.24
		8	8.95	8.64	9.61	12.94	12.73	12.18

TABLE D-2-continued

Degradant Content After Storage (% w/w of enalapril maleate)

	Storage		Formulation					
	° C.	Weeks	D1	D2	D3	D4	D5	D6
		12	11.01	10.64	11.41	16.16		
		26	17.18	17.11	18.30	27.36		

Example E: Stability of Solution Formulations of Enalapril Maleate

Solution formulations were prepared according to Table E-1. Thirty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5° C.±3° C., at room temperature (19-23° C.) and at 40° C.±2° C. At various times, bottles were removed from the storage condition and analyzed.

Composition of Enalapril Maleate Formulations (mg/mL)

Component	E1	E2	E3	E4	E5	E6
Enalapril maleate	1.00	1.00	1.00	1.00	1.00	1.00
Xylitol	150	200		150		
Citric acid anhydrous	3.29	3.29	3.29	3.29	1.65	0.82
Sodium citrate anhydrous	0.75	0.75	0.75	0.75	0.38	0.19
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00
Sucralose			0.70		0.70	0.70
Mixed berry flavor	0.50		0.50	0.50	0.50	0.50
Water	qs	qs	qs	qs	qs	qs
pH (measured)	3.3	3.3	3.3	3.4	3.3	3.3

qs = sufficient quantity

The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table E-2.

TABLE E-2

Degradant Content After Storage (% w/w of enalapril maleate)

	Storage		Formulation					
	° C.	Weeks	E1	E2	E3	E4	E5	E6
Diketopi-perazine	5	0	0.01	0.01	0.01	0.01	0.01	0.01
		4	0.04	0.04	0.05	0.04	0.03	0.03
		8	0.04	0.04	0.04	0.04	0.03	0.03
		12	0.05	0.05	0.04	0.05	0.04	0.04
		26	0.07	0.06	0.05	0.06	0.05	0.05
		52					0.15	0.14
		62	0.18	0.18	0.16	0.14		
	19-23	0	0.01	0.01	0.01	0.01	0.01	0.01
		4	0.22	0.23	0.21	0.20	0.16	0.15
		8	0.35	0.35	0.32	0.31	0.29	0.28
		12	0.58	0.59	0.53	0.51	0.48	0.45
		26	1.10	1.10	1.00	0.95	0.97	0.92
		52					2.30	2.15
		62	3.02	3.04	2.75	2.64		
	40	0	0.01	0.01	0.01	0.01	0.01	0.01
		4	2.65	2.71	2.60	2.42	1.76	1.68
		8	4.02	3.99	3.99	3.62	3.37	3.13
		12	6.72	6.42	6.47	6.00	5.53	5.29
Enalaprilat	5	0	0.00	0.00	0.01	0.02	0.00	0.00
		4	0.07	0.09	0.10	0.11	0.07	0.08
		8	0.12	0.14	0.10	0.13	0.09	0.08
		12	0.16	0.15	0.15	0.17	0.14	0.11
		26	0.31	0.30	0.29	0.31	0.27	0.24
		52					0.54	0.46
		62	0.75	0.75	0.74	0.71		
	19-23	0	0.00	0.00	0.01	0.02	0.00	0.00
		4	0.65	0.65	0.68	0.70	0.50	0.46
		8	1.17	1.19	1.20	1.23	1.03	0.95
		12	1.67	1.69	1.72	1.80	1.30	1.21
		26	3.36	3.38	3.42	3.57	3.07	2.90
		52					6.32	5.88
		62	7.99	8.02	8.04	8.57		
	40	0	0.00	0.00	0.01	0.02	0.00	0.00
		4	4.85	4.93	5.19	5.42	3.33	3.25
		8	8.08	8.06	8.56	9.01	6.65	6.35
		12	10.70	10.48	11.01	11.97	8.14	7.96

Example F: Effect of pH on the Formation of Degradants in Enalapril Formulations at 5° C. and 19-23° C.

The content of enalapril diketopiperazine and enalaprilat that were formed after 8 weeks of storage for formulations C1-C3 and D1-D5 are plotted in FIG. **1** (5° C.±3° C.) and FIG. **2** (19-23° C. storage). These formulations all contained 20 mM total citrate buffer content, but with varying pH. The general effects of formulation pH on the formation of the two main enalapril degradants are shown.

Example G: Antimicrobial Effectiveness Testing of Enalapril Maleate Formulations at pH 3.3

Enalapril formulations were prepared containing differing amounts of the antimicrobial preservative, sodium benzoate. The formulations were then tested for antimicrobial effectiveness (AET) according to the procedures in the 2014 United States Pharmacopeia 37, Chapter <51> for category 3 products. The formulation of the formulations and the AET results are included in Table G-1.

TABLE G-1

Formulation and AET Testing Results

	Formulation				
	G1	G2	G3	G4	G5
Formulation (mg/mL)					
Enalapril maleate	1.00	1.00	1.00	1.00	1.00
Xylitol	150	150	150	150	
Sucralose					0.70
Citric acid, anhydrous	1.64	1.64	1.64	1.64	1.80
Sodium citrate, anhydrous	0.322	0.322	0.322	0.322	
Sodium citrate, dihydrate					0.165
Sodium benzoate	1.00	0.80	0.60	0.40	1.0
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50
Water	q.s.	q.s.	q.s.	q.s.	q.s.
HCl/NaOH	as need to achieve pH				
Measured pH	3.3	3.3	3.3	3.3	3.3
AET Results					
USP <51>	Pass	Pass	Pass	Pass	Pass

qs = sufficient quantity

Example H: Clinical Trial: Bioavailability Study of 10 mg Enalapril Maleate Oral Solution Vs. 10 mg Epaned® Powder for Oral Solution (Reconstituted) Under Fasted Conditions

The objective of this open-label, randomized, two-period, two-treatment, two-way crossover study was to compare the oral bioavailability of a test formulation of 10 mL of enalapril maleate oral solution, 1 mg/mL (formulation E-5), to an equivalent oral dose of the commercially available comparator product, Epaned® (enalapril maleate) Powder for Oral Solution, 1 mg/mL, when administered under fasted conditions in healthy adults.

Study design: Thirty-two healthy adult subjects received a single 10 mL dose of enalapril maleate oral solution, 1 mg/mL, formulation E-5 (Treatment A), in one period and a separate single dose of Epaned Powder for Oral Solution (reconstituted with the supplied Ora-Sweet SF), 1 mg/mL (Treatment B) in another period. Each treatment was administered after an overnight fast of at least 10 hours, followed by a 4-hour fast postdose. Each treatment was administered via a 10 mL oral dosing syringe and followed with 240 mL of room temperature tap water. Each drug administration was separated by a washout period of at least 7 days.

During each study period, meals were the same and scheduled at approximately the same times relative to dose. In addition, during each period, blood samples were obtained prior to and following each dose at selected times through 72 hours postdose. Pharmacokinetic samples were analyzed for enalapril and its metabolite enalaprilat using a validated analytical method; appropriate pharmacokinetic parameters were calculated for each formulation using non-compartmental methods. Blood was also drawn and urine collected for clinical laboratory testing at screening and at the end of the study.

Statistical Methods: The concentration-time data were analyzed using noncompartmental methods in Phoenix™ WinNonlin® (Version 6.3, Pharsight Corporation). Concentration-time data that were below the limit of quantitation (BLQ) were treated as zero in the data summarization and descriptive statistics. In the pharmacokinetic analysis, BLQ concentrations were treated as zero from time-zero up to the time at which the first quantifiable concentration was observed; embedded and/or terminal BLQ concentrations

were treated as "missing". Actual sample times were used for all pharmacokinetic and statistical analyses. Analysis of variance (ANOVA) and the Schuirmann's two one-sided t-test procedures at the 5% significance level were applied to the log-transformed pharmacokinetic exposure parameters, C_{max}, AUC_{last}, and AUC_{inf}. The 90% confidence interval for the ratio of the geometric means (Test/Reference) was calculated. Bioequivalence was declared if the lower and upper confidence intervals (CIs) of the log-transformed parameters were within 80% to 125% for enalapril and enalaprilat.

Results: A total of 32 subjects participated in the study and 29 of these subjects completed both study periods. Based on the geometric mean ratios of enalapril and enalaprilat AUCs (AUC_{last} and AUC_{inf}), the bioavailability of the enalapril maleate oral solution (formulation E-5) relative to the Epaned Powder for Oral Solution (reconstituted) was approximately 105% to 110%. The geometric mean ratios of enalapril and enalaprilat C_{max} were approximately 115% and 1090, respectively. The 90% CI for comparing the maximum exposure to enalapril and enalaprilat, based on in (C_{max}), was within the accepted 80% to 125% limits. The 90% CIs for comparing total systemic exposure to enalapril and enalaprilat, based on in (AUC_{last}) and in (AUC_{inf}), was within the accepted 80% to 125% limits. Therefore, the test formulation of enalapril maleate oral solution, 1 mg/mL, is bioequivalent to the reference product, Epaned Powder for Oral Solution (reconstituted), 1 mg/mL, under fasted conditions.

While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

What is claimed is:

1. A stable oral liquid formulation, consisting essentially of:

(i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;

(ii) a sweetener;

(iii) a preservative, wherein the preservative comprises sodium benzoate, a paraben or a mixture of parabens;

(iv) water; and

(v) optionally a flavoring agent;

wherein the formulation is stable at about 5±3° C. for at least 12 months; and

wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

2. The stable oral liquid formulation of claim **1**, wherein the formulation is stable at about 5±3° C. for at least 18 months.

3. The stable oral liquid formulation of claim **1**, wherein the formulation is stable at about 5±3° C. for at least 24 months.

4. The stable oral liquid formulation of claim **1**, wherein the formulation maintains a pH between about 3 and about 4 for at least 3 months at about 5±3° C.

5. The stable oral liquid formulation of claim **1**, wherein the formulation maintains a pH between about 3 and about 4 for at least 12 months at about 5±3° C.

6. The stable oral liquid formulation of claim **1**, wherein the sweetener is sucralose.

7. The stable oral liquid formulation of claim **6**, wherein the sucralose is present in about 0.5 mg/ml to about 0.9 mg/ml in the oral liquid formulation.

8. The stable oral liquid formulation of claim **1**, wherein the sweetener is saccharin or a salt thereof.

9. The stable oral liquid formulation of claim **8**, wherein the saccharin or a salt thereof is present at about 2 mg/ml in the oral liquid formulation.

10. The stable oral liquid formulation of claim **1**, comprising a flavoring agent.

11. The stable oral liquid formulation of claim **1**, wherein the enalapril or a pharmaceutically acceptable salt or solvate thereof functions as a buffer.

12. The stable oral liquid formulation of claim **1**, wherein the enalapril or a pharmaceutically acceptable salt or solvate thereof is present at about 1.0 mg/ml in the oral liquid formulation.

13. The stable oral liquid formulation of claim **1**, wherein the preservative is a mixture of parabens.

14. The stable oral liquid formulation of claim **1**, wherein the paraben or the mixture of parabens is methylparaben, ethylparaben, propylparaben, butylparaben, salts thereof, or a combination thereof.

15. The stable oral liquid formulation of claim **1**, wherein the mixture of parabens comprises methylparaben and propylparaben.

16. The stable oral liquid formulation of claim **1**, wherein the paraben or the mixture of parabens is present at about 0.1 mg/ml to about 2 mg/ml in the oral liquid formulation.

17. The stable oral liquid formulation of claim **1**, wherein the preservative comprises sodium benzoate.

18. The stable oral liquid formulation of claim **17**, wherein the sodium benzoate is present at about 0.2 mg/ml to about 1.2 mg/ml in the oral liquid formulation.

19. The stable oral liquid formulation of claim **1**, consisting essentially of:

(i) about 1.0 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;

(ii) a sweetener that is sucralose or sodium saccharin;

(iii) a preservative, wherein the preservative comprises a mixture of parabens that is present at about 0.1 mg/ml to about 2 mg/ml in the oral liquid formulation;

(iv) water; and

(v) optionally a flavoring agent.

20. The stable oral liquid formulation of claim **1**, consisting essentially of:

(i) about 1.0 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;

(ii) a sweetener that is sucralose or sodium saccharin;

(iii) a preservative, wherein the preservative comprises sodium benzoate that is present at about 0.2 mg/ml to about 1.2 mg/ml in the oral liquid formulation;

(iv) water; and

(v) optionally a flavoring agent.

* * * * *

Exhibit B

US011141405B2

(12) **United States Patent**
Mosher et al.

(10) **Patent No.: US 11,141,405 B2**
(45) **Date of Patent: *Oct. 12, 2021**

(54) **ENALAPRIL FORMULATIONS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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(22) Filed: **Apr. 12, 2021**

(65) **Prior Publication Data**

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Related U.S. Application Data

(63) Continuation of application No. 17/150,587, filed on Jan. 15, 2021, now Pat. No. 11,040,023, which is a continuation of application No. 16/991,575, filed on Aug. 12, 2020, now Pat. No. 10,918,621, which is a continuation of application No. 16/883,553, filed on May 26, 2020, now Pat. No. 10,799,476, which is a continuation of application No. 16/242,898, filed on Jan. 8, 2019, now Pat. No. 10,772,868, which is a

(Continued)

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A61K 9/00	(2006.01)
A61K 47/26	(2006.01)
A61K 47/12	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 31/401*** (2013.01); ***A61K 9/0053*** (2013.01); ***A61K 9/0095*** (2013.01); ***A61K 47/12*** (2013.01); ***A61K 47/26*** (2013.01)

(58) **Field of Classification Search**

CPC A61K 31/401; A61K 47/12; A61K 47/26; A61K 9/0053; A61K 9/0095

See application file for complete search history.

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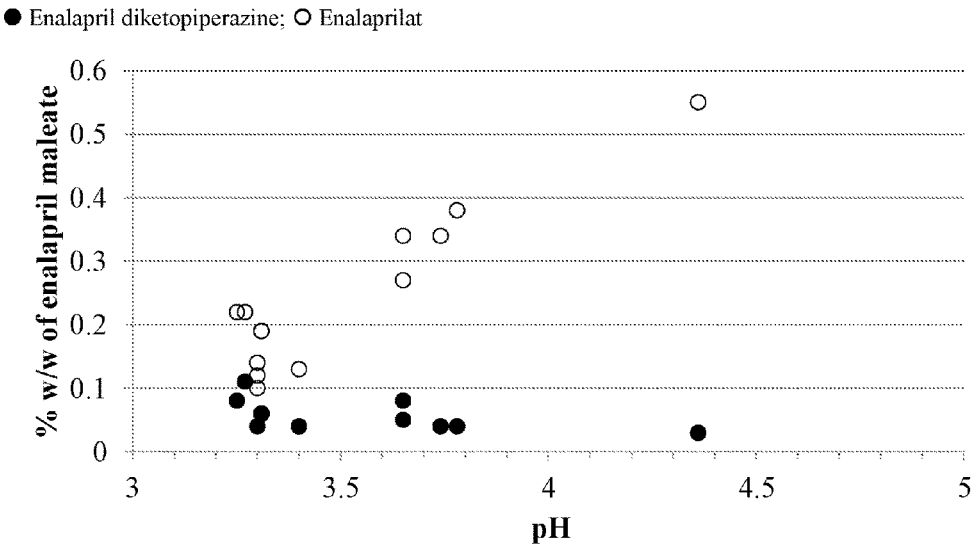
(57) **ABSTRACT**

Provided herein are stable enalapril oral liquid formulations. Also provided herein are methods of using enalapril oral liquid formulations for the treatment of certain diseases including hypertension, heart failure and asymptomatic left ventricular dysfunction.

23 Claims, 2 Drawing Sheets



Related U.S. Application Data

continuation of application No. 16/177,159, filed on Oct. 31, 2018, now Pat. No. 10,786,482, which is a continuation of application No. 16/003,994, filed on Jun. 8, 2018, now Pat. No. 10,154,987, which is a continuation of application No. 15/802,341, filed on Nov. 2, 2017, now Pat. No. 10,039,745, which is a continuation of application No. 15/613,622, filed on Jun. 5, 2017, now Pat. No. 9,808,442, which is a continuation of application No. 15/081,603, filed on Mar. 25, 2016, now Pat. No. 9,669,008.

(60) Provisional application No. 62/310,198, filed on Mar. 18, 2016.

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FIG. 1

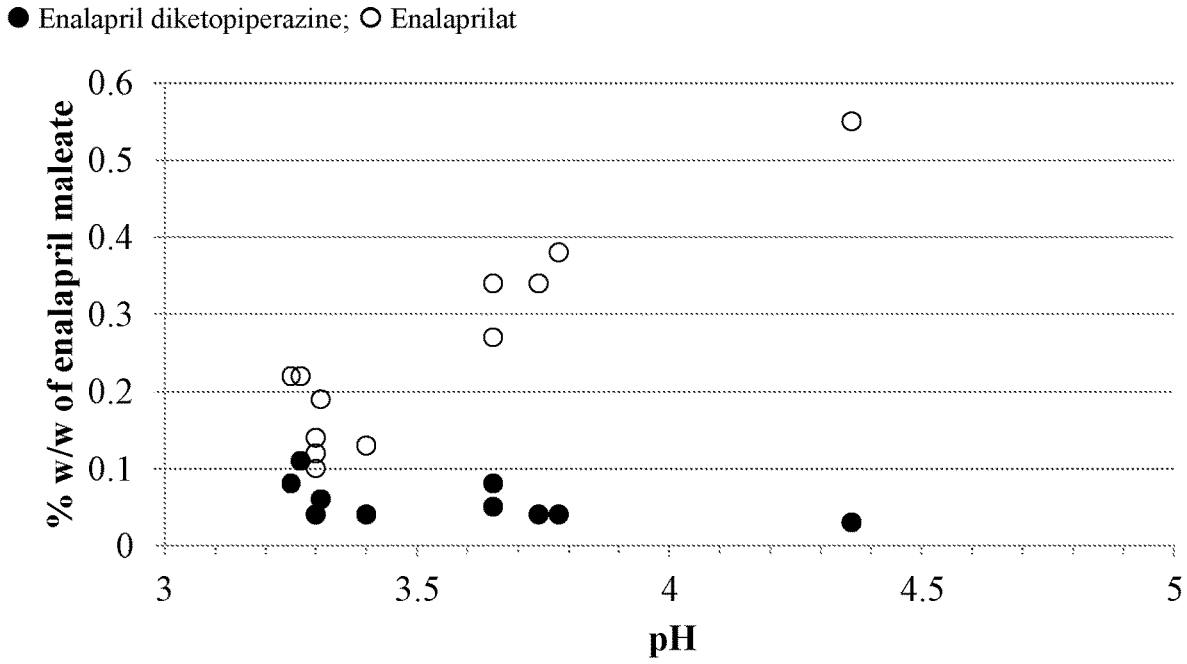
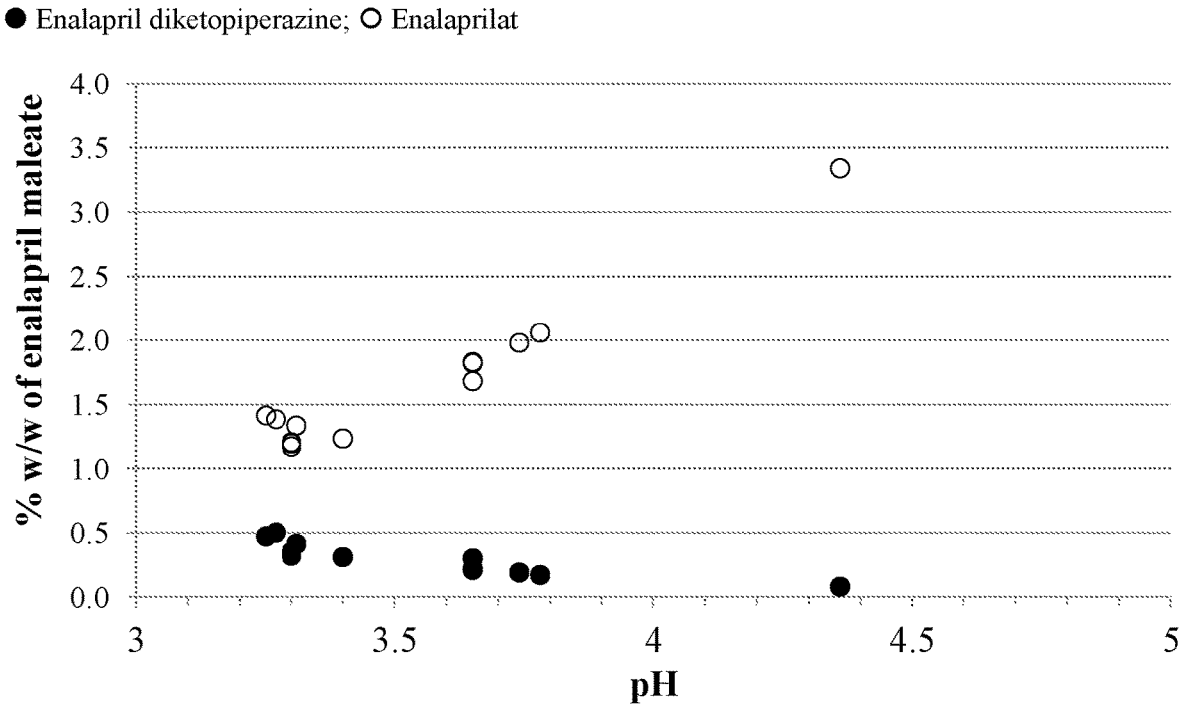

● Enalapril diketopiperazine; ○ Enalaprilat
% w/w of enalapril maleate
0.6
0.5
0.4
0.3
0.2
0.1
0
3
3.5
4
4.5
5
pH

FIG. 2


● Enalapril diketopiperazine; ○ Enalaprilat
% w/w of enalapril maleate
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
3
3.5
4
4.5
5
pH

ENALAPRIL FORMULATIONS

CROSS-REFERENCE OF RELATED APPLICATIONS

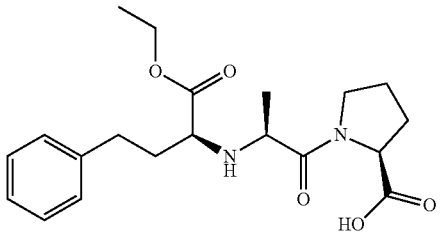
This application is a continuation of U.S. patent application Ser. No. 17/150,587, filed Jan. 15, 2021 which is a continuation of Ser. No. 16/991,575, filed Aug. 12, 2020 which is a continuation of Ser. No. 16/883,553, filed May 26, 2020 which is a continuation of U.S. patent application Ser. No. 16/242,898, filed Jan. 8, 2019, which is a continuation of Ser. No. 16/177,159, filed Oct. 31, 2018, which is a continuation of U.S. patent application Ser. No. 16/003,994, filed Jun. 8, 2018 (now U.S. Pat. No. 10,154,987, issued Dec. 18, 2018), which is a continuation of U.S. patent application Ser. No. 15/802,341, filed Nov. 2, 2017 (now U.S. Pat. No. 10,039,745, issued Aug. 7, 2018), which is a continuation of U.S. patent application Ser. No. 15/613,622, filed Jun. 5, 2017 (now U.S. Pat. No. 9,808,442, issued Nov. 7, 2017), which is a continuation of U.S. patent application Ser. No. 15/081,603, filed Mar. 25, 2016 (now U.S. Pat. No. 9,669,008, issued Jun. 6, 2017), which claims the benefit of U.S. Provisional Patent Application No. 62/310,198, filed Mar. 18, 2016, all of which are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

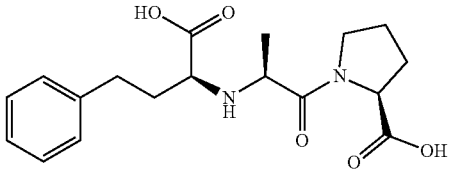
Hypertension, or high blood pressure, is a serious health issue in many countries. According to the National Heart Blood and Lung Institute, it is thought that about 1 in 3 adults in the United States alone have hypertension. Left unchecked, hypertension is considered a substantial risk factor for cardiovascular and other diseases including coronary heart disease, myocardial infarction, congestive heart failure, stroke and kidney failure. Hypertension is classified as primary (essential) hypertension or secondary hypertension. Primary hypertension has no known cause and may be related to a number of environmental, lifestyle and genetic factors such as stress, obesity, smoking, inactivity and sodium intake. Secondary hypertension can be caused by drug or surgical interventions, or by abnormalities in the renal, cardiovascular or endocrine system.

A number of antihypertensive drugs are available for treating hypertension. Various therapeutic classes of antihypertensive drugs include alpha-adrenergic blockers, beta-adrenergic blockers, calcium-channel blockers, hypotensives, mineralcorticoid antagonists, central alpha-agonists, diuretics and rennin-angiotensin-aldosterone inhibitors which include angiotensin II receptor antagonists (ARB) and angiotensin-converting enzyme (ACE) inhibitors. Angiotensin-converting enzyme (ACE) inhibitors inhibit angiotensin-converting enzyme (ACE), a peptydyl dipeptidase that catalyzes angiotension I to angiotension II, a potent vasoconstrictor involved in regulating blood pressure.

Enalapril is a prodrug belonging to the angiotensin-converting enzyme (ACE) inhibitor of medications. It is rapidly hydrolyzed in the liver to enalaprilat following oral administration. Enalaprilat acts as a potent inhibitor of ACE. The structural formulae of enalapril and enalaprilat are as follows:



Enalapril



Enalaprilat

Enalapril is currently administered in the form of oral tablets, (e.g., Vasotec®) or in the form of liquid formulations obtained by reconstitution of enalapril powder formulations. In addition to the treatment of hypertension, enalapril tablets have been used for symptomatic congestive heart failure, and asymptomatic left ventricular dysfunction.

SUMMARY OF THE INVENTION

Provided herein are enalapril oral liquid formulations. In one aspect, the enalapril oral liquid formulation, comprises (i) enalapril or a pharmaceutically acceptable salt or solvate thereof; (ii) a sweetener that is sucralose (iii) a buffer comprising citric acid; (iv) a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5±3° C. for at least 12 months.

In some embodiments, the enalapril is enalapril maleate. In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer in the formulation further comprises sodium citrate dihydrate. In some embodiments, the amount of enalapril or a pharmaceutically acceptable salt or solvate thereof is about 0.6 to about 1.2 mg/ml. In some embodiments, the amount of sucralose is about 0.5 to about 0.9 mg/ml. In some embodiments, the amount of citric acid in the buffer is about 0.8 to about 3.5 mg/ml. In some embodiments, the amount of sodium citrate dihydrate in the buffer is about 0.1 to about 0.80 mg/ml. In some embodiments, the amount of the sodium benzoate is about 0.2 to about 1.2 mg/ml. In some embodiments, the amount of enalapril or a pharmaceutically acceptable salt or solvate thereof is about 10 to about 25% (w/w of solids). In some embodiments, the amount of sucralose is about 8 to about 18% (w/w of solids). In some embodiments, the amount of citric acid in the buffer is about 17 to about 47% (w/w of solids). In some embodiments, the amount of sodium citrate dihydrate in the buffer is about 1 to about 11% (w/w of solids). In some embodiments, the amount of sodium benzoate is about 12 to about 25% (w/w of solids). In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about 5±3° C. for at least 18 months.

In some embodiments, the formulation is stable at about 5±3° C. for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In one aspect, the enalapril oral liquid formulation, comprises (i) about 1 mg/ml enalapril maleate; (ii) about 0.70 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5±3° C. for at least 12 months.

In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer further comprises about 0.15 mg/mL sodium citrate dihydrate. In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about 5±3° C. for at least 18 months. In some embodiments, the formulation is stable at about 5±3° C. for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In one aspect, the enalapril oral liquid formulation comprises (i) about 19.3% (w/w of solids) enalapril maleate; (ii) about 13.5% (w/w of solids) of a sweetener that is sucralose; (iii) a buffer comprising about 35.2% (w/w of solids) citric acid; (iv) about 19.3% (w/w of solids) of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5±3° C. for at least 12 months.

In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer further comprises about 2.9% (w/w of solids) sodium citrate dihydrate. In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about 5±3° C. for at least 18 months. In some embodiments, the formulation is stable at about 5±3° C. for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In one aspect, the enalapril oral liquid formulation consists essentially of (i) about 1 mg/ml enalapril maleate; (ii) about 0.70 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; (v) a flavoring agent; and (vi) water; wherein the pH of the formulation is less than about 3.5 adjusted by sodium hydroxide or hydrochloric acid; and wherein the formulation is stable at about 5±3° C. for at least 12 months.

Also provided herein are methods of treating hypertension in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.7 mg/ml sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5±3° C. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In some embodiments, the hypertension is primary (essential) hypertension. In some embodiments, the hypertension is secondary hypertension. In some embodiments, the subject has blood pressure values greater than or equal to 140/90 mmm Hg. In some embodiments, the subject is an adult. In some embodiments, the subject is elderly. In some embodiments, the subject is a child. In some embodiments, the formulation is administered to the subject in a fasted state. In some embodiments, the formulation is administered to the subject in a fed state. In some embodiments, the formulation is further administered in combination with an agent selected from the group consisting of diuretics, beta blockers, alpha blockers, mixed alpha and beta blockers, calcium channel blockers, angiotensin II receptor antagonists, ACE inhibitors, aldosterone antagonists, and alpha-2 agonists.

Also provided herein are methods of treating prehypertension in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.7 mg/ml of a sweetener that is sucralose; (ii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5±3° C. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In some embodiments, the subject has blood pressure values of about 120-139/80-89 mm Hg.

Also provided herein are methods of treating heart failure in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.70 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5±3° C. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

Also provided herein are methods of treating left ventricular dysfunction in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.7 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5±3° C. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

INCORPORATION BY REFERENCE

All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication,

patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

FIG. **1**: Effect of pH on degradant formation after 8 weeks of storage of various enalapril solution formulations at 5° C.

FIG. **2**: Effect of pH on degradant formation after 8 weeks of storage of various enalapril solution formulations at room temperature (19-22° C.).

DETAILED DESCRIPTION OF THE INVENTION

Provided herein are stable enalapril oral liquid formulations. Also provided herein are stable enalapril powder formulations for reconstitution for oral liquid administration. These enalapril formulations described herein are useful for the treatment of hypertension, prehypertension, heart failure as well as ventricular dysfunction. The formulations are advantageous over conventional solid dosage administration of enalapril ranging from ease of administration, accuracy of dosing, accessibility to additional patient populations such as to children and the elderly, and an increased patient compliance to medication.

It is generally known that certain segments of the population have difficulty ingesting and swallowing solid oral dosage forms such as tablets and capsules. As many as a quarter of the total population has this difficulty. Often, this leads to non-compliance with the recommended medical therapy with the solid dosage forms, thereby resulting in rending the therapy ineffective. Further, solid dosage forms are not recommended for children or elderly due to increased risk in choking.

Furthermore, the dose of enalapril to be given to children is calculated according to the child's weight. When the calculated dose is something other than the amount present in one or more intact solid dosage forms, the solid dosage form must be divided to provide the correct dose. This leads to inaccurate dosing when solid dosages forms, such as tablets, are compounded to prepare other formulations for children.

For enalapril, one solution to overcoming the use of the tablet form is for a compounding pharmacist to pulverize and crush the enalapril tablet(s) into a powder via mortar and pestle and reconstitute the powder in some liquid form. However forming a enalapril oral liquid in this fashion has significant drawbacks including large variability in the actual dosage, incomplete solubilizing of the enalapril tablet in the liquid, rapid instability, inconsistent formulation methods per compounding pharmacy, and a number of other potential issues. The crushed tablet liquid formulation may also be potentially unsafe due to contamination with residual drugs and other substances from the mortar and pestle or other crushing agent.

Alternatively, enalapril is formulated as enalapril powder compositions for reconstitution as oral liquids as described in U.S. Pat. No. 8,568,747. The powder compositions as described in this patent require mannitol and colloidal silicon dioxide for stability and dissolution. While these powder compositions are an improvement over crushing tablets, they still require a step of mixing with a diluent. The stable enalapril oral liquid formulations described herein require no extra steps or manipulation prior to administration to a subject. Further, the stable enalapril oral liquid formulations described herein do not require or need mannitol or colloidal silicon dioxide for stability and dissolution.

The present embodiments described herein provide a safe and effective oral administration of enalapril for the treatment of hypertension and other disorders. In particular, the embodiments provide stable enalapril oral liquid formulations as well as alternatively enalapril powder formulations for oral liquid administration.

As used herein, "enalapril" refers to enalapril base, its salt, or solvate or derivative or isomer or polymorph thereof. Suitable compounds include the free base, the organic and inorganic salts, isomers, isomer salts, solvates, polymorphs, complexes etc. U.S. Pat. Nos. 4,374,829; 4,472,380 and 4,510,083 disclose exemplary methods in the preparation of enalapril. In some embodiments, the enalapril used in the formulations described herein is an enalapril salt. In some instances, the enalapril salt is enalapril maleate. In other instances, the enalapril salt is in the form of enalapril sodium.

Other ACE inhibitors are contemplated in the formulations within and include but are not limited to quinapril, indolapril, ramipril, perindopril, lisinopril, benazepril, imidapril, zofenopril, trandolapril, fosinopril, captopril, and their salts, solvates, derivatives, polymorphs, or complexes, thereof.

Enalapril Oral Liquid Formulations

Oral liquids include, but are not limited to, solutions (both aqueous and nonaqueous), suspensions, emulsions, syrups, slurries, juices, elixirs, dispersions, and the like. It is envisioned that solution/suspensions are also included where certain components described herein are in a solution while other components are in a suspension.

In one aspect, the enalapril liquid formulations described herein comprise enalapril, a preservative, a sweetening agent, a buffer, and water. In one embodiment, the sweetening agent is sucralose. In one embodiment, the sweetening agent is xylitol. In one embodiment, the sweetening agent is not mannitol. In another embodiment, the preservative is sodium benzoate. In some embodiments, the preservative is a paraben. In some embodiments, the preservative is a mixture of parabens. In yet another embodiment, the buffer comprises citric acid. In some embodiments, the buffer further comprises sodium citrate. In one aspect, the enalapril liquid formulation described herein comprises enalapril, sucralose, sodium benzoate, citric acid, sodium citrate, and water. In some embodiments, the enalapril liquid formulation herein further comprises a flavoring agent. In some embodiments, the enalapril liquid formulation is not obtained from crushing enalapril tablet and dissolving the powder in a suitable vehicle for oral administration. In some embodiments, the enalapril liquid formulation does not contain silicon dioxide. In some embodiments, the enalapril liquid formulation does not contain mannitol. In some embodiments, the enalapril liquid formulation does not contain lactose. In some embodiments, the enalapril liquid formulation does not contain magnesium stearate. In some embodiments, the enalapril liquid formulation does not contain sodium bicarbonate. In some embodiments, the enalapril liquid formulation does not contain iron oxides.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.6 to about 1.2 mg/ml in the oral liquid formulation. In other embodiments,

enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/ml, about 0.91 mg/ml, about 0.92 mg/ml, about 0.93 mg/ml, about 0.94 mg/ml, about 0.95 mg/ml, about 0.96 mg/ml, about 0.97 mg/ml, about 0.98 mg/ml, about 0.99 mg/ml, about 1 mg/ml, about 1.01 mg/ml, about 1.02, mg/ml, about 1.03 mg/ml, about 1.04 mg/ml, about 1.05 mg/ml, about 1.06 mg/ml, about 1.07 mg/ml, about 1.08 mg/ml, about 1.09 mg/ml, about 1.1 mg/ml, about 1.11 mg/ml, about 1.12, mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, or about 1.2 mg/ml in the liquid oral formulation. In some embodiments, enalapril is present in about 0.76 mg/ml in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 1 mg/ml in the oral liquid formulation. In some embodiments, the formulation contains enalapril or another pharmaceutically acceptable salt of enalapril in a molar concentration equivalent to 1 mg/mL enalapril maleate. In some embodiments, the formulation contains enalapril or another pharmaceutically acceptable salt of enalapril in a molar concentration equivalent to 0.76 mg/mL enalapril.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5 w/w to about 30% w/w of the solids in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5 w/w, about 1 w/w, about 1.5% w/w, about 2% w/w, about 2.5 w/w, about 3% w/w, about 3.5 w/w, about 4% w/w, about 4.5% w/w, about 5 w/w, about 5.5 w/w, about 6% w/w, about 6.5 w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5 w/w, about 9% w/w, about 9.5 w/w, about 10% w/w, about 10.5% w/w, about 11 w/w, about 11.5 w/w, about 12% w/w, about 12.5 w/w, about 13% w/w, about 13.5 w/w, about 14% w/w, about 14.5 w/w, about 15 w/w, about 15.1% w/w, about 15.2% w/w, about 15.3% w/w, about 15.4% w/w, about 15.5 w/w, about 15.6% w/w, about 15.7% w/w, about 15.8% w/w, about 15.9% w/w, about 16% w/w, about 16.1% w/w, about 16.2% w/w, about 16.3% w/w, about 16.4% w/w, about 16.5 w/w, about 16.6% w/w, about 16.7% w/w, about 16.8% w/w, about 16.9% w/w, about 17% w/w, about 17.1% w/w, about 17.2% w/w, about 17.3% w/w, about 17.4% w/w, about 17.5 w/w, about 17.6% w/w, about 17.7% w/w, about 17.8% w/w, about 17.9% w/w, about 18% w/w, about 18.1% w/w, about 18.2% w/w, about 18.3% w/w, about 18.4% w/w, about 18.5% w/w, about 18.6% w/w, about 18.7% w/w, about 18.8% w/w, about 18.9% w/w, about 19% w/w, about 19.1% w/w, about 19.2% w/w, about 19.3% w/w, about 19.4% w/w, about 19.5 w/w, about 19.6% w/w, about 19.7% w/w, about 19.8% w/w, about 19.9% w/w, about 20% w/w, about 20.1% w/w, about 20.2% w/w, about 20.3% w/w, about 20.4% w/w, about 20.5 w/w, about 20.6% w/w, about 20.7% w/w, about 20.8% w/w, about 20.9% w/w, about 21% w/w, about 21.1% w/w, about 21.2% w/w, about 21.3% w/w, about 21.4% w/w, about 21.5 w/w, about 21.6% w/w, about 21.7% w/w, about 21.8% w/w, about 21.9% w/w, about 22% w/w, about 22.5 w/w, about 23% w/w, about 23.5 w/w, about 24% w/w, about 24.5% w/w, about 25% w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 10% w/w to about 25% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 10.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 15% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 18.2% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 13.5 w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 19.3% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 24.5 w/w of the solids in the oral liquid formulation.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w to about 1 w/w of the solids in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w, about 0.15% w/w, about 0.2% w/w, about 0.25% w/w, about 0.3% w/w, about 0.35% w/w, about 0.4% w/w, about 0.45% w/w, about 0.5% w/w, about 0.55% w/w, about 0.6% w/w, about 0.65% w/w, about 0.7% w/w, about 0.75% w/w, about 0.8% w/w, about 0.85% w/w, about 0.9% w/w, about 0.95% w/w, or about 1% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.4% w/w to about 0.7% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 0.4% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 0.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 0.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 0.6% w/w of the solids in the oral liquid formulation.

Sweetener in the Enalapril Oral Liquid Formulations

Sweeteners or sweetening agents include any compounds that provide a sweet taste. This includes natural and synthetic sugars, natural and artificial sweeteners, natural extracts and any material that initiates a sweet sensation in a subject. In some embodiments, a solid/powder sweetener is used in the oral liquid formulation described herein. In other embodiments, a liquid sweetener is used in the oral liquid formulation described herein.

Sugars illustratively include glucose, fructose, sucrose, xylitol, tagatose, sucralose, maltitol, isomaltulose, Isomalt™ (hydrogenated isomaltulose), lactitol, sorbitol, erythritol, trehalose, maltodextrin, polydextrose, and the like. Other sweeteners illustratively include glycerin, inulin, erythritol, maltol, acesulfame and salts thereof, e.g., acesulfame potassium, alitame, aspartame, neotame, sodium cyclamate, saccharin and salts thereof, e.g., saccharin sodium or saccharin calcium, neohesperidin dihydrochalcone, stevioside, thaumatin, and the like. Sweeteners can be used in the form of crude or refined products such as hydrogenated starch hydrolysates, maltitol syrup, high fructose corn syrup, etc., and as branded products, e.g., Sweet Am™ liquid (Product Code 918.003-propylene glycol, ethyl alcohol, and proprietary artificial flavor combination, Flavors of North America) and Sweet Am™ powder (Product Code 918.005—maltodextrin, sorbitol, and fructose combination

and Product Code 918.010—water, propylene glycol, sorbitol, fructose, and proprietary natural and artificial flavor combination, Flavors of North America), ProSweet™ (1-10% proprietary plant/vegetable extract and 90-99% dextrose combination, Viriginia Dare), Maltisweet™ (maltitol solution, Ingredion), Sorbo™ (sorbitol and sorbitol/xylitol solution, SPI Polyols), Invertose™ (high fructose corn syrup, Ingredion), Rebalance M60 and X60 (sucralose and maltodextrin, Tate and Lyle), and Ora-Sweet® sugar-free flavored syrup (Paddock Laboratories, Inc.). Sweeteners can be used singly or in combinations of two or more. Suitable concentrations of different sweeteners can be selected based on published information, manufacturers' data sheets and by routine testing.

In some embodiments, the enalapril oral liquid formulation described herein comprises a sweetening agent. In some embodiments, the sweetening agent is sucralose. In some embodiments, the sweetening agent is xylitol. In some embodiments, the sweetener is not mannitol.

In some embodiments, the enalapril oral liquid formulation described herein comprises sucralose. In some embodiments, sucralose is present in about 0.5 to about 0.9 mg/ml in the oral liquid formulation. In other embodiments, sucralose is present in about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml, about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.60 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.70 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.80 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, or about 0.90 mg/ml in the oral liquid formulation. In some embodiments, sucralose is present in about 0.7 mg/ml in the oral liquid formulation.

In some embodiments, sucralose is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5 w/w, about 3% w/w, about 3.5 w/w, about 4% w/w, about 4.5% w/w, about 5 w/w, about 5.5 w/w, about 6% w/w, about 6.5 w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5 w/w, about 9% w/w, about 9.5 w/w, about 10% w/w, about 10.5% w/w, about 11 w/w, about 11.5 w/w, about 12% w/w, about 12.5 w/w, about 13% w/w, about 13.5 w/w, about 14% w/w, about 14.5 w/w, about 15 w/w, about 15.5 w/w, about 16% w/w, about 16.5 w/w, about 17% w/w, about 17.5 w/w, about 18% w/w, about 18.5 w/w, about 19% w/w, about 19.5 w/w, about 20% w/w, about 20.5 w/w, about 21% w/w, about 21.5 w/w, about 22% w/w, about 22.5 w/w, about 23% w/w, about 23.5 w/w, about 24% w/w, about 24.5 w/w, about 25 w/w, about 25.5 w/w, about 26% w/w, about 26.5 w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5 w/w, about 29% w/w, about 29.5 w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 8% w/w to about 18% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 9.5 w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 13.5 w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 16.5% w/w of the solids in the oral liquid formulation.

In some embodiments, the enalapril oral liquid formulation described herein comprises xylitol. In some embodiments, xylitol is present in about 140 mg/ml to about 210 mg/ml in the oral liquid formulation.

In some embodiments, xylitol is present in about 140 mg/ml, about 145 mg/ml, about 150 mg/ml, about 155 mg/ml, about 160 mg/ml, about 165 mg/ml, about 170 mg/ml, about 175 mg/ml, about 180 mg/ml, about 185 mg/ml, about 190 mg/ml, about 195 mg/ml, about 200 mg/ml, about 205 mg/ml, or about 210 mg/ml of the oral liquid formulation. In some embodiments, xylitol is present in about 150 mg/ml in the oral liquid formulation. In some embodiments, xylitol is present in about 200 mg/ml in the oral liquid formulation.

In some embodiments, xylitol is present in about 80% w/w to about 99% w/w of the solids in the oral liquid formulation. In other embodiments, xylitol is present in about 80% w/w, about 81% w/w, about 82% w/w, about 83% w/w, about 84% w/w, about 85 w/w, about 86% w/w, about 87% w/w, about 88% w/w, about 89% w/w, about 90% w/w, about 91% w/w, about 92% w/w, about 93% w/w, about 94% w/w, about 95 w/w, about 96% w/w, about 97% w/w, about 98% w/w, or about 99% w/w of the solids in the oral liquid formulation. In some embodiments, xylitol is present in about 96% w/w to about 98% w/w of the solids in the oral liquid formulation. In some embodiments, xylitol is present in about 96% w/w of the solids in the oral liquid formulation.

Preservative in the Enalapril Oral Liquid Formulations

Preservatives include anti-microbials, anti-oxidants, and agents that enhance sterility. Exemplary preservatives include ascorbic acid, ascorbyl palmitate, BHA, BHT, citric acid, EDTA and its salts, erythorbic acid, fumaric acid, malic acid, propyl gallate, sodium ascorbate, sodium bisulfate, sodium metabisulfite, sodium sulfite, parabens (such as methylparaben, ethylparaben, propylparaben, butylparaben and their salts), benzoic acid, sodium benzoate, potassium sorbate, vanillin, and the like.

In some embodiments, the enalapril oral liquid formulation described herein comprises a preservative.

In some embodiments, the preservative is a paraben and the sweetener is not a sugar (such as, but not limited to glucose, fructose, sucrose, lactose, maltose) or a sugar alcohol (such as, but not limited to xylitol, mannitol, lactitol, maltitol, sorbitol).

In some embodiments, the preservative is sodium benzoate.

In some embodiments, modulation of the pH is desired to provide the best antimicrobial activity of the preservative, sodium benzoate. In some embodiments, the antimicrobial activity of sodium benzoate drops when the pH is increased above 5.

In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, or about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3.3.

In some embodiments, sodium benzoate is present in about 0.2 to about 1.2 mg/ml in the oral liquid formulation.

In other embodiments, sodium benzoate is present in about 0.2 mg/ml, about 0.21 mg/ml, about 0.22 mg/ml, about 0.23 mg/ml, about 0.24 mg/ml, about 0.25 mg/ml, about 0.26 mg/ml, about 0.27 mg/ml, about 0.28 mg/ml, about 0.29 mg/ml, about 0.3 mg/ml, about 0.31 mg/ml, about 0.32 mg/ml, about 0.33 mg/ml, about 0.34 mg/ml, about 0.35 mg/ml, about 0.36 mg/ml, about 0.37 mg/ml, about 0.38 mg/ml, about 0.39 mg/ml, about 0.4 mg/ml, about 0.41 mg/ml, about 0.42 mg/ml, about 0.43 mg/ml, about 0.44 mg/ml, about 0.45 mg/ml, about 0.46 mg/ml, about 0.47 mg/ml, about 0.48 mg/ml, about 0.49 mg/ml, about 0.5 mg/ml, about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml, about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/ml, about 0.91 mg/ml, about 0.92 mg/ml, about 0.93 mg/ml, about 0.94 mg/ml, about 0.95 mg/ml, about 0.96 mg/ml, about 0.97 mg/ml, about 0.98 mg/ml, about 0.99 mg/ml, about 1 mg/ml, about 1.01 mg/ml, about 1.02, mg/ml, about 1.03 mg/ml, about 1.04 mg/ml, about 1.05 mg/ml, about 1.06 mg/ml, about 1.07 mg/ml, about 1.08 mg/ml, about 1.09 mg/ml, about 1.1 mg/ml, about 1.11 mg/ml, about 1.12, mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, or about 1.2 mg/ml in the liquid oral formulation. In some embodiments, sodium benzoate is present in about 1 mg/ml in the oral liquid formulation.

In some embodiments, sodium benzoate is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 1% w/w, about 1.5 w/w, about 2% w/w, about 2.5 w/w, about 3% w/w, about 3.5 w/w, about 4% w/w, about 4.5 w/w, about 5 w/w, about 5.5 w/w, about 6% w/w, about 6.5 w/w, about 7% w/w, about 7.5 w/w, about 8% w/w, about 8.5 w/w, about 9% w/w, about 9.5 w/w, about 10% w/w, about 10.5 w/w, about 11 w/w, about 11.5 w/w, about 12% w/w, about 12.5 w/w, about 13% w/w, about 13.5 w/w, about 14% w/w, about 14.5 w/w, about 15 w/w, about 15.1% w/w, about 15.2% w/w, about 15.3% w/w, about 15.4% w/w, about 15.5 w/w, about 15.6% w/w, about 15.7% w/w, about 15.8% w/w, about 15.9% w/w, about 16% w/w, about 16.1% w/w, about 16.2% w/w, about 16.3% w/w, about 16.4% w/w, about 16.5 w/w, about 16.6% w/w, about 16.7% w/w, about 16.8% w/w, about 16.9% w/w, about 17% w/w, about 17.1% w/w, about 17.2% w/w, about 17.3% w/w, about 17.4% w/w, about 17.5 w/w, about 17.6% w/w, about 17.7% w/w, about 17.8% w/w, about 17.9% w/w, about 18% w/w, about 18.1% w/w, about 18.2% w/w, about 18.3% w/w, about 18.4% w/w, about 18.5 w/w, about 18.6% w/w, about 18.7% w/w, about 18.8% w/w, about 18.9% w/w, about 19% w/w, about 19.1% w/w, about 19.2% w/w, about 19.3% w/w, about 19.4% w/w, about 19.5% w/w, about 19.6% w/w, about 19.7% w/w, about 19.8% w/w, about 19.9% w/w, about 20% w/w, about 20.1% w/w, about 20.2% w/w, about 20.3% w/w, about 20.4% w/w, about 20.5 w/w, about 20.6% w/w, about 20.7% w/w, about 20.8% w/w, about 20.9% w/w, about 21% w/w, about 21.1% w/w, about 21.2% w/w, about 21.3% w/w, about 21.4% w/w, about 21.5 w/w, about 21.6% w/w, about 21.7% w/w, about 21.8% w/w, about 21.9% w/w, about 22% w/w, about 22.5 w/w, about 23% w/w, about 23.5 w/w, about 24% w/w, about 24.5 w/w, about 25 w/w, about 25.5 w/w, about 26% w/w, about 26.5 w/w, about 27% w/w, about 27.5 w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5 w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 10% w/w to about 25 w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 13.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 19.3% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 23.5% w/w of the solids in the oral liquid formulation.

In some embodiments, sodium benzoate is present in about 0.1% w/w to about 1% w/w of the solids in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 0.1% w/w, about 0.15% w/w, about 0.2% w/w, about 0.25% w/w, about 0.3% w/w, about 0.35% w/w, about 0.4% w/w, about 0.45% w/w, about 0.5% w/w, about 0.55% w/w, about 0.6% w/w, about 0.65% w/w, about 0.7% w/w, about 0.75% w/w, about 0.8% w/w, about 0.85% w/w, about 0.9% w/w, about 0.95% w/w, or about 1% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.4% w/w to about 0.7% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.45% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.6% w/w of the solids in the oral liquid formulation.

In some embodiments, sodium benzoate is present in an amount sufficient to provide antimicrobial effectiveness to the enalapril oral liquid formulation described herein. (See Table G-1).

In some embodiments, the preservative is a paraben. In some embodiments, the preservative is a mixture of parabens. In some embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml to about 2 mg/ml in the oral liquid formulation. In other embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml, about 0.2 mg/ml, about 0.3 mg/ml, about 0.4 mg/ml, about 0.5 mg/ml, about 0.6 mg/ml, about 0.7 mg/ml, about 0.8 mg/ml, about 0.9 mg/ml, about 1 mg/ml, about 1.1 mg/ml, about 1.2 mg/ml, about 1.3 mg/ml, about 1.4 mg/ml, or about 1.5 mg/ml, about 1.6 mg/ml, about 1.7 mg/ml, about 1.8 mg/ml, about 1.9 mg/ml, or about 2 mg/ml in the liquid oral formulation. In some embodiments, the paraben or mixture of parabens is present in about 1.6 mg/ml to about 2 mg/ml in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 1.6 mg/ml to about 1.8 mg/ml in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml to about 0.5 mg/ml in the oral liquid formulation.

In some embodiments, the paraben or mixture of parabens is present in about 2% w/w to about 30% w/w of the solids in the oral liquid formulation. In other embodiments, the paraben or mixture of parabens is present in about 2% w/w, about 3% w/w, about 4% w/w, about 5% w/w, about 6% w/w, about 7% w/w, about 8% w/w, about 9% w/w, about 10% w/w, about 11% w/w, about 12% w/w, about 13% w/w, about 14% w/w, about 15% w/w, about 16% w/w, about 17% w/w, about 18% w/w, about 19% w/w, about 20% w/w, about 21% w/w, about 22% w/w, about 23% w/w, about 24% w/w, about 25% w/w, about 26% w/w, about 27% w/w,

about 28% w/w, about 29% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 2% w/w to about 3% w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 23% w/w to about 26% w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 26% w/w to about 30% w/w of the solids in the oral liquid formulation.

Sweetener and Preservative Incompatibility

Paraben preservatives (especially methylparaben) can react with selected sugars (glucose, fructose, sucrose, lactose, maltose) and sugar alcohols (xylitol, mannitol, lactitol, maltitol, sorbitol) to form transesterification reaction products. This can be undesirable from a formulation and stability standpoint as the transesterification creates additional degradants.

In some embodiments, the enalapril oral liquid formulation described herein does not comprise a paraben preservative. In further embodiments, the enalapril oral liquid formulation described herein does not comprise a paraben preservative when the formulation also comprises a sugar or sugar alcohol.

pH of Enalapril Oral Liquid Formulations

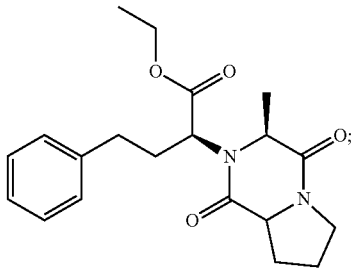
Buffering agents maintain the pH of the liquid enalapril formulation. Non-limiting examples of buffering agents include, but are not limited to sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium glucomate, aluminum hydroxide, aluminum hydroxide/sodium bicarbonate co-precipitate, mixture of an amino acid and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer. Additional buffering agents include citric acid, sodium citrate, sodium tartarate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, sodium acetate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, and other calcium salts. Some buffering agents also impart effervescent qualities when a powder is reconstituted in a solution. In some embodiments, the buffering agent is not sodium bicarbonate.

In some embodiments, the oral liquid formulation comprises a buffer.

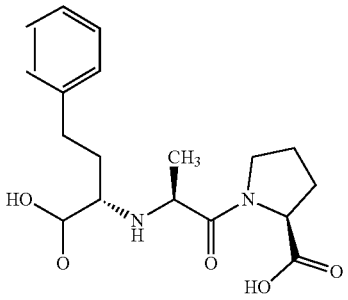
In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid and sodium citrate. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid and sodium citrate dihydrate or an equivalent molar amount of sodium citrate anhydrous. In some embodiments, the sodium citrate is monosodium citrate. In some embodiments, the sodium citrate is disodium citrate. In some embodiments, the sodium citrate is trisodium citrate.

In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises phosphoric acid. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises sodium phosphate.

In some embodiments, modulation of the pH is desired to provide a lowered impurity profile. In the exemplary stability studies, the main enalapril degradants are enalapril diketopiperazine and enalaprilat:



enalapril diketopiperazine



enalaprilat

In some embodiments, the percentage of enalaprilat formation is increased when the pH is above 3.5. (See table C-2 and FIG. **1** and FIG. **2**). In some embodiments, the percentage of enalapril diketopiperazine formation is slightly increased as the pH is below 4.

In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, or about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3.3.

In some embodiments, the formation of degradants is dependent on the buffer concentration. In some embodiments, the buffer concentration impacts the taste of the enalapril oral liquid formulation.

In some embodiments, the buffer concentration is between about 5 mM and about 20 mM. In some embodiments, the buffer concentration is about 5 mM, about 6 mM, about 7 mM, about 8 mM, about 9 mM, about 10 mM, about 11 mM, about 12 mM, about 13 mM, about 14 mM, about 15 mM, about 16 mM, about 17 mM, about 18 mM, about 19 mM, or about 20 mM. In some embodiments, the buffer concentration is about 5 mM. In some embodiments, the buffer concentration is about 10 mM. In some embodiments, the buffer concentration is about 20 mM.

In some embodiments, citric acid is present in about 0.7 to about 2 mg/ml in the oral liquid formulation. In other

embodiments, citric acid is present in about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/mL, about 0.91 mg/mL, about 0.92 mg/mL, about 0.93 mg/mL, about 0.94 mg/mL, about 0.95 mg/mL, about 0.96 mg/mL, about 0.97 mg/mL, about 0.98 mg/mL, about 0.99 mg/mL, about 1 mg/mL, about 1.11 mg/ml, about 1.12 mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, about 1.2 mg/ml, about 1.21 mg/ml, about 1.22 mg/ml, about 1.23 mg/ml, about 1.24 mg/ml, about 1.25 mg/ml, about 1.26 mg/ml, about 1.27 mg/ml, about 1.28 mg/ml, about 1.29 mg/ml, about 1.3 mg/mL, about 1.31 mg/mL, about 1.32 mg/mL, about 1.33 mg/mL, about 1.34 mg/mL, about 1.35 mg/mL, about 1.36 mg/mL, about 1.37 mg/mL, about 1.38 mg/mL, about 1.39 mg/mL, about 1.4 mg/ml, about 1.41 mg/ml, about 1.42 mg/ml, about 1.43 mg/ml, about 1.44 mg/ml, about 1.45 mg/ml, about 1.46 mg/ml, about 1.47 mg/ml, about 1.48 mg/ml, about 1.49 mg/ml, about 1.5 mg/ml, about 1.51 mg/ml, about 1.52 mg/ml, about 1.53 mg/ml, about 1.54 mg/ml, about 1.55 mg/ml, about 1.56 mg/ml, about 1.57 mg/ml, about 1.58 mg/ml, about 1.59 mg/ml, about 1.6 mg/mL, about 1.61 mg/mL, about 1.62 mg/mL, about 1.63 mg/mL, about 1.64 mg/mL, about 1.65 mg/mL, about 1.66 mg/mL, about 1.67 mg/mL, about 1.68 mg/mL, about 1.69 mg/mL, about 1.7 mg/ml, about 1.71 mg/ml, about 1.72 mg/ml, about 1.73 mg/ml, about 1.74 mg/ml, about 1.75 mg/ml, about 1.76 mg/ml, about 1.77 mg/ml, about 1.78 mg/ml, about 1.79 mg/ml, about 1.8 mg/ml, about 1.81 mg/ml, about 1.82 mg/ml, about 1.83 mg/ml, about 1.84 mg/ml, about 1.85 mg/ml, about 1.86 mg/ml, about 1.87 mg/ml, about 1.88 mg/ml, about 1.89 mg/ml, about 1.9 mg/mL, about 1.91 mg/mL, about 1.92 mg/mL, about 1.93 mg/mL, about 1.94 mg/mL, about 1.95 mg/mL, about 1.96 mg/mL, about 1.97 mg/mL, about 1.98 mg/mL, about 1.99 mg/mL, or about 2 mg/mL in the oral liquid formulation. In some embodiments, citric acid is present in about 1.65 mg/ml in the oral liquid formulation. In some embodiments, citric acid is present in about 1.82 mg/ml in the oral liquid formulation. In some embodiments, citric acid is present in about 0.82 mg/ml in the oral liquid formulation.

In some embodiments, citric acid is present in about 2 to about 3.5 mg/ml in the oral liquid formulation. In other embodiments, citric acid is present in about 2 mg/mL, about 2.05 mg/mL, about 2.1 mg/mL, about 2.15 mg/mL, about 2.2 mg/mL, about 2.25 mg/mL, about 2.3 mg/mL, about 2.35 mg/mL, about 2.4 mg/mL, about 2.45 mg/mL, about 2.5 mg/mL, about 2.55 mg/mL, about 2.6 mg/mL, about 2.65 mg/mL, about 2.7 mg/mL, about 2.75 mg/mL, about 2.8 mg/mL, about 2.85 mg/mL, about 2.9 mg/mL, about 2.95 mg/mL, about 3 mg/mL, about 3.05 mg/ml, about 3.1 mg/mL, about 3.15 mg/mL, about 3.2 mg/mL, about 3.25 mg/mL, about 3.3 mg/mL, about 3.35 mg/mL, about 3.4 mg/mL, about 3.45 mg/mL, or about 3.5 mg/mL in the oral liquid formulation. In some embodiments, citric acid is present in about 3.3 mg/ml in the oral liquid formulation.

In some embodiments, citric acid is present in about 10% w/w to about 50 w/w of the solids in the oral liquid formulation. In other embodiments, citric acid is present in about 10% w/w, about 11% w/w, about 12% w/w, about 13% w/w, about 14% w/w, about 15 w/w, about 16% w/w, about 17% w/w, about 18% w/w, about 19% w/w, about 20% w/w, about 21% w/w, about 22% w/w, about 23% w/w, about 24% w/w, about 25 w/w, about 26% w/w, about 27% w/w, about 28% w/w, about 29% w/w, about 30% w/w, about 31% w/w, about 32% w/w, about 33% w/w, about 34% w/w, about 35% w/w, about 36% w/w, about 37% w/w, about 38% w/w, about 39% w/w, about 40% w/w, about 41% w/w, about 42% w/w, about 43% w/w, about 44% w/w, about 45 w/w, about 46% w/w, about 47% w/w, about 48% w/w, about 49% w/w, about 50% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 45 w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 31% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 35 w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 19% w/w of the solids in the oral liquid formulation.

In some embodiments, citric acid is present in about 1 w/w to about 5 w/w of the solids in the oral liquid formulation. In other embodiments, citric acid is present in about 1% w/w, about 1.1% w/w, about 1.2% w/w, about 1.3% w/w, about 1.4% w/w, about 1.5 w/w, about 1.6% w/w, about 1.7% w/w, about 1.8% w/w, about 1.9% w/w, about 2% w/w, about 2.1% w/w, about 2.2% w/w, about 2.3% w/w, about 2.4% w/w, about 2.5 w/w, about 2.6% w/w, about 2.7% w/w, about 2.8% w/w, about 2.9% w/w, about 3% w/w, about 3.1% w/w, about 3.2% w/w, about 3.3% w/w, about 3.4% w/w, about 3.5 w/w, about 3.6% w/w, about 3.7% w/w, about 3.8% w/w, about 3.9% w/w, about 4% w/w, about 4.1% w/w, about 4.2% w/w, about 4.3% w/w, about 4.4% w/w, about 4.5 w/w, about 4.6% w/w, about 4.7% w/w, about 4.8% w/w, about 4.9% w/w, or about 5 w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 2.1% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 1.6% w/w of the solids in the oral liquid formulation.

In some embodiments, sodium citrate dihydrate is present in about 0.1 to about 0.8 mg/ml in the oral liquid formulation. In other embodiments, sodium citrate dihydrate is present in the oral liquid formulation is about 0.1 mg/mL, about 0.11 mg/mL, about 0.12 mg/mL, about 0.13 mg/mL, about 0.14 mg/mL, about 0.15 mg/ml, about 0.16 mg/mL, about 0.17 mg/mL, about 0.18 mg/mL, about 0.19 mg/mL, about 0.2 mg/ml, about 0.21 mg/ml, about 0.22 mg/ml, about 0.23 mg/ml, about 0.24 mg/ml, about 0.25 mg/ml, about 0.26 mg/ml, about 0.27 mg/ml, about 0.28 mg/ml, about 0.29 mg/ml, about 0.3 mg/ml, about 0.31 mg/ml, about 0.32 mg/ml, about 0.33 mg/ml, about 0.34 mg/ml, about 0.35 mg/ml, about 0.36 mg/ml, about 0.37 mg/ml, about 0.38 mg/ml, about 0.39 mg/ml, about 0.4 mg/ml, about 0.41 mg/ml, about 0.42 mg/ml, about 0.43 mg/ml, about 0.44 mg/ml, about 0.45 mg/ml, about 0.46 mg/ml, about 0.47 mg/ml, about 0.48 mg/ml, about 0.49 mg/ml, about 0.5 mg/ml, about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml, about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, or about 0.8 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.75 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.35

mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.2 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.15 mg/ml in the oral liquid formulation.

In some embodiments, sodium citrate dihydrate is present in about 1 w/w to about 15% w/w of the solids in the oral liquid formulation. In other embodiments, sodium citrate dihydrate is present in about 1 w/w, about 1.1% w/w, about 1.2% w/w, about 1.3% w/w, about 1.4% w/w, about 1.5% w/w, about 1.6% w/w, about 1.7% w/w, about 1.8% w/w, about 1.9% w/w, about 2% w/w, about 2.1% w/w, about 2.2% w/w, about 2.3% w/w, about 2.4% w/w, about 2.5 w/w, about 2.6% w/w, about 2.7% w/w, about 2.8% w/w, about 2.9% w/w, about 3% w/w, about 3.1% w/w, about 3.2% w/w, about 3.3% w/w, about 3.4% w/w, about 3.5 w/w, about 3.6% w/w, about 3.7% w/w, about 3.8% w/w, about 3.9% w/w, about 4% w/w, about 4.5 w/w, about 5 w/w, about 5.5 w/w, about 6% w/w, about 6.5 w/w, about 7% w/w, about 7.5 w/w, about 8% w/w, about 8.5 w/w, about 9% w/w, about 9.5 w/w, about 10% w/w, about 10.5 w/w, about 11 w/w, about 11.5 w/w, about 12% w/w, about 12.5 w/w, about 13% w/w, about 13.5 w/w, about 14% w/w, about 14.5 w/w, about 15 w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 10.5 w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 7.5 w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 4.5 w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 2.9% w/w of the solids in the oral liquid formulation.

In other embodiments, sodium citrate dihydrate is not added to the formulation.

Additional Excipients

In further embodiments, the enalapril liquid formulation described herein comprises additional excipients including, but not limited to, glidants, flavoring agents, coloring agents and thickeners. Additional excipients such as bulking agents, tonicity agents and chelating agents are within the scope of the embodiments.

Glidants are substances that improve flowability of a powder. Suitable glidants include, but are not limited to, calcium phosphate tribasic, calcium silicate, cellulose (powdered), colloidal silicon dioxide, magnesium silicate, magnesium trisilicate, silicon dioxide, starch, talc and the like. In some embodiments, the enalapril powder formulations described herein comprise a glidant. In some embodiments the glidant is not colloidal silicon dioxide.

In another embodiment, the enalapril liquid formulation comprises a flavoring agent or flavorant to enhance the taste or aroma of the formulation in liquid form. Suitable natural or synthetic flavoring agents can be selected from standard reference books, for example Fenaroli's Handbook of Flavor Ingredients, 3rd edition (1995). Non-limiting examples of suitable natural flavors, some of which can readily be simulated with synthetic agents or combinations thereof, include almond, anise, apple, apricot, bergamot, blackberry, blackcurrant, blueberry, cacao, caramel, cherry, cinnamon, clove, coffee, coriander, cranberry, cumin, dill, *eucalyptus*, fennel, fig, ginger, grape, grapefruit, guava, hop, lemon, licorice, lime, malt, mandarin, molasses, nutmeg, mixed berry, orange, peach, pear, peppermint, pineapple, raspberry, rose, spearmint, strawberry, tangerine, tea, vanilla, wintergreen, etc. Also useful, particularly where the formulation is intended primarily for pediatric use, is tutti-frutti or bubblegum flavor, a compounded flavoring agent based on fruit flavors. Presently preferred flavoring agents include anise, cinnamon, cacao, orange, peppermint, cherry (in particular wild cherry), grape, bubblegum, vanilla, and mixed berry. In some embodiments, the enalapril liquid formulation described herein comprises a mixed berry flavoring agent. Flavoring agents can be used singly or in combinations of two or more.

In further embodiments, the enalapril liquid formulation comprises a coloring agent for identity and/or aesthetic purposes. Suitable coloring agents illustratively include FD&C Red No. 3, FD&C Red No. 20, FD&C Red No. 40, FD&C Yellow No. 6, FD&C Blue No. 2, FD&C Green No. 5, FD&C Orange No. 5, caramel, ferric oxide and mixtures thereof.

Thickeners impart viscosity or weight to the resultant liquid forms from the enalapril formulation described herein. Exemplary thickeners include dextrin, cellulose derivatives (carboxymethylcellulose and its salts, ethylcellulose, hydroxyethyl cellulose, methylcellulose, hypromellose, and the like) starches, pectin, polyethylene glycol, polyethylene oxide, trehalose and certain gums (xanthan gum, locust bean gum, etc.). In certain embodiments, the enalapril liquid formulation comprises a thickener.

Additional excipients are contemplated in the enalapril liquid formulation embodiments. These additional excipients are selected based on function and compatibility with the enalapril liquid formulations described herein and may be found, for example in *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, (Easton, Pa.: Mack Publishing Co 1975); Liberman, H. A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms* (New York, N.Y.: Marcel Decker 1980); and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed (Lippincott Williams & Wilkins 1999), herein incorporated by reference in their entirety.

Stability

The main enalapril degradants are enalapril diketopiperazine and enalaprilat.

The enalapril oral liquid formulations described herein are stable in various storage conditions including refrigerated, ambient and accelerated conditions. Stable as used herein refers to enalapril oral liquid formulations having about 95% or greater of the initial enalapril amount and about 5 w/w or less total impurities or related substances at the end of a given storage period. The percentage of impurities is calculated from the amount of impurities relative to the amount of enalapril. Stability is assessed by HPLC or any other known testing method. In some embodiments, the stable enalapril oral liquid formulations have about 5% w/w, about 4% w/w, about 3% w/w, about 2.5% w/w, about 2% w/w, about 1.5% w/w, about 1% w/w, or about 0.5% w/w total impurities or related substances. In other embodiments, the stable enalapril oral liquid formulations have about 5% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 4% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 3% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 2% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 1% w/w total impurities or related substances.

At refrigerated condition, the enalapril oral liquid formulations described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 6 months, at least

9 months, at least 12 months, at least 15 months, at least 18 months, at least 24 months, at least 30 months and at least 36 months. In some embodiments, refrigerated condition is 5±3° C. In some embodiments, refrigerated condition is about 2° C., about 2.1° C., about 2.2° C., about 2.3° C., about 2.4° C., about 2.5° C., about 2.6° C., about 2.7° C., about 2.8° C., about 2.9° C., about 3° C., about 3.1° C., about 3.2° C., about 3.3° C., about 3.4° C., about 3.5° C., about 3.6° C., about 3.7° C., about 3.8° C., about 3.9° C., about 4° C., about 4.1° C., about 4.2° C., about 4.3° C., about 4.4° C., about 4.5° C., about 4.6° C., about 4.7° C., about 4.8° C., about 4.9° C., about 5° C., about 5.1° C., about 5.2° C., about 5.3° C., about 5.4° C., about 5.5° C., about 5.6° C., about 5.7° C., about 5.8° C., about 5.9° C., about 6° C., about 6.1° C., about 6.2° C., about 6.3° C., about 6.4° C., about 6.5° C., about 6.6° C., about 6.7° C., about 6.8° C., about 6.9° C., about 7° C., about 7.1° C., about 7.2° C., about 7.3° C., about 7.4° C., about 7.5° C., about 7.6° C., about 7.7° C., about 7.8° C., about 7.9° C., or about 8° C. At accelerated conditions, the enalapril oral liquid formulations described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months or at least 12 months. Accelerated conditions for the enalapril oral liquid formulations described herein include temperature and/or relative humidity (RH) that are at or above ambient levels (e.g. 25±5° C.; 55±10% RH). In some instances, an accelerated condition is at about 25° C., about 30° C., about 35° C., about 40° C., about 45° C., about 50° C., about 55° C. or about 60° C. In other instances, an accelerated condition is above 55% RH, about 65% RH, about 70% RH, about 75% RH or about 80% RH. In further instances, an accelerated condition is about 40° C. or 60° C. at ambient humidity. In yet further instances, an accelerated condition is about 40° C. at 75±5% RH humidity.

Enalapril Oral Powder Formulation

In another aspect, enalapril oral liquid formulations described herein are prepared from the reconstitution of an enalapril powder formulation. In some embodiments, the enalapril powder formulation comprising enalapril, a sweetener, a preservative, and optionally an excipient is dissolved in water, a buffer, other aqueous solvent, or a liquid to form an enalapril oral liquid formulation. In one embodiment, the sweetening agent is sucralose. In one embodiment, the sweetener is not mannitol. In one embodiment, the sweetening agent is xylitol. In another embodiment, the preservative is sodium benzoate. In one embodiment, the preservative is a paraben preservative. In one aspect, the enalapril powder formulation described herein comprises enalapril, sucralose, and sodium benzoate. In some embodiments, the enalapril powder formulation herein further comprises a flavoring agent. In some embodiments, the enalapril powder formulation herein further comprises one or more buffering agents.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w to about 30% w/w of the powder formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w, about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5 w/w, about 15 w/w, about 15.5 w/w, about 16% w/w, about 16.5 w/w, about 17% w/w, about 17.5 w/w, about 18% w/w, about 18.5 w/w, about 19% w/w, about 19.5 w/w, about 20% w/w, about 20.5 w/w, about 21% w/w, about 21.5 w/w, about 22% w/w, about 22.5 w/w, about 23% w/w, about 23.5 w/w, about 24% w/w, about 24.5 w/w, about w/w, about 25.5 w/w, about 26% w/w, about 26.5 w/w, about 27% w/w, about 27.5 w/w, about 28% w/w, about 28.5 w/w, about 29% w/w, about 29.5 w/w, or about 30% w/w of the powder formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 10% w/w to about 25 w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 13.5 w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 19.5 w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 24.5 w/w of the powder formulation. In some embodiments, enalapril is present in about 10.5 w/w of the powder formulation. In some embodiments, enalapril is present in about 14.5 w/w of the powder formulation. In some embodiments, enalapril is present in about 18% w/w of the powder formulation.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w to about 1 w/w of the powder formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w, about 0.15 w/w, about 0.2% w/w, about 0.25 w/w, about 0.3% w/w, about 0.35 w/w, about 0.4% w/w, about 0.45 w/w, about 0.5 w/w, about 0.55 w/w, about 0.6% w/w, about 0.65 w/w, about 0.7% w/w, about 0.75 w/w, about 0.8% w/w, about 0.85 w/w, about 0.9% w/w, about 0.95 w/w, or about 1 w/w of the powder formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.4% w/w to about 0.7% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 0.45 w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 0.6% w/w of the powder formulation. In some embodiments, enalapril is present in about 0.4% w/w of the powder formulation. In some embodiments, enalapril is present in about 0.5 w/w of the powder formulation.

Various amounts and concentrations of other components (sweeteners, buffers, preservatives, and the like) in the enalapril powder formulations are found in the previous section describing the amounts and concentrations for the analogous enalapril oral liquid formulations. For example, in some embodiments where sucralose is present in about 1 w/w to about 30% w/w of the solids in the oral liquid formulation; in an analogous enalapril powder formulation, sucralose would be about 1 w/w to about 30% w/w in the powder formulation. In some embodiments where sodium benzoate is present in about 1 w/w to about 30% w/w of the solids in the oral liquid formulation, in an analogous enalapril powder formulation sodium benzoate is present in about 1 w/w to about 30% w/w in the powder formulation.

Liquid vehicles suitable for the enalapril powder formulations to be reconstituted into an oral solution described herein are selected for a particular oral liquid formulation (solution, suspension, etc.) as well as other qualities such as clarity, toxicity, viscosity, compatibility with excipients, chemical inertness, palatability, odor, color and economy. Exemplary liquid vehicles include water, ethyl alcohol, glycerin, propylene glycol, syrup (sugar or other sweetener based, e.g., Ora-Sweet® SF sugar-free flavored syrup), juices (apple, grape, orange, cranberry, cherry, tomato and the like), other beverages (tea, coffee, soft drinks, milk and

the like), oils (olive, soybean, corn, mineral, castor and the like), and combinations or mixtures thereof. Certain liquid vehicles, e.g., oil and water, can be combined together to form emulsions. In some embodiments, water is used for as a vehicle for a enalapril oral liquid formulation. In other embodiments, a syrup is used for as a vehicle for a enalapril oral liquid formulation. In yet other embodiments, a juice is used for as a vehicle for a enalapril oral liquid formulation.

Buffering agents maintain the pH of the liquid enalapril formulation. Non-limiting examples of buffering agents include, but are not limited to sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium gluconate, aluminum hydroxide, aluminum hydroxide/sodium bicarbonate co precipitate, mixture of an amino acid and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer. Additional buffering agents include citric acid, sodium citrate, sodium tartrate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, sodium acetate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, and other calcium salts. Some buffering agents also impart effervescent qualities when a powder is reconstituted in a solution.

In some embodiments, the reconstituted oral liquid formulation comprises a buffer. In some embodiments, the buffer comprises citric acid and sodium citrate.

In further embodiments, the enalapril powder formulation described herein comprises additional excipients including, but not limited to, glidants, flavoring agents, coloring agents and thickeners. Additional excipients such as bulking agents, tonicity agents and chelating agents are within the scope of the embodiments.

Glidants are substances that improve flowability of a powder. Suitable glidants include, but are not limited to, calcium phosphate tribasic, calcium silicate, cellulose (powdered), colloidal silicon dioxide, magnesium silicate, magnesium trisilicate, silicon dioxide, starch, talc and the like. In some embodiments, the enalapril powder formulations described herein comprise a glidant.

In another embodiment, the enalapril powder formulation described herein comprises a flavoring agent or flavorant to enhance the taste or aroma of the formulation in liquid form. Suitable natural or synthetic flavoring agents can be selected from standard reference books, for example Fenaroli's Handbook of Flavor Ingredients, 3rd edition (1995). Non-limiting examples of suitable natural flavors, some of which can readily be simulated with synthetic agents or combinations thereof, include almond, anise, apple, apricot, bergamot, blackberry, blackcurrant, blueberry, cacao, caramel, cherry, cinnamon, clove, coffee, coriander, cranberry, cumin, dill, *eucalyptus*, fennel, fig, ginger, grape, grapefruit, guava, hop, lemon, licorice, lime, malt, mandarin, molasses, nutmeg, mixed berry, orange, peach, pear, peppermint, pineapple, raspberry, rose, spearmint, strawberry, tangerine, tea, vanilla, wintergreen, etc. Also useful, particularly where the formulation is intended primarily for pediatric use, is tutti-frutti or bubblegum flavor, a compounded flavoring agent based on fruit flavors. Presently preferred flavoring agents include anise, cinnamon, cacao, orange, peppermint, cherry (in particular wild cherry), grape, bubblegum, vanilla, and mixed berry. Flavoring agents can be used singly or in combinations of two or more.

In further embodiments, the enalapril powder formulation described herein comprises a coloring agent for identity and/or aesthetic purposes. Suitable coloring agents illustratively include FD&C Red No. 3, FD&C Red No. 20, FD&C Red No. 40, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, caramel, ferric oxide and mixtures thereof.

In further embodiments, the enalapril powder formulation described herein comprises a thickener. Thickeners impart viscosity or weight to the resultant liquid forms from the enalapril formulation described herein. Exemplary thickeners include dextrin, cellulose derivatives (carboxymethylcellulose and its salts, ethylcellulose, hydroxyethyl cellulose, methylcellulose, hypromellose, and the like) starches, pectin, polyethylene glycol, polyethylene oxide, trehalose and certain gums (xanthan gum, locust bean gum, etc.).

Additional excipients are contemplated in the enalapril powder formulation embodiments. These additional excipients are selected based on function and compatibility with the enalapril powder formulation described herein and may be found, for example in *Remington: The Science and Practice of Pharmacy*, Nineteeth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, (Easton, Pa.: Mack Publishing Co 1975); Liberman, H. A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms* (New York, N.Y.: Marcel Decker 1980); and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed (Lippincott Williams & Wilkins 1999), herein incorporated by reference in their entirety.

In some embodiments, the enalapril oral liquid formulation prepared from the powder formulations described herein are homogenous. Homogenous liquids as used herein refer to those liquids that are uniform in appearance, identity, consistency and drug concentration per volume. Non-homogenous liquids include such liquids that have varied coloring, viscosity and/or aggregation of solid particulates, as well as non-uniform drug concentration in a given unit volume. Homogeneity in liquids are assessed by qualitative identification or appearance tests and/or quantitative HPLC testing or the like. The mixing methods and excipients described herein are selected to impart a homogenous quality to a resultant enalapril oral liquid formulation.

Mixing methods encompass any type of mixing that result in a homogenous enalapril oral liquid formulation. In some embodiments, a quantity of an enalapril powder formulation is added to a liquid vehicle and then mixed by a stirring, shaking, swirling, agitation element or a combination thereof. In certain instances, a fraction of a enalapril powder formulation (i.e., one-half, one-third, one-fourth, etc.) is added to a liquid vehicle, mixed by stirring, shaking, swirling, agitation or a combination thereof, and the subsequent powder fraction(s) is added and mixed. In other embodiments, a liquid vehicle is added to an enalapril powder formulation in a container, for example, a bottle, vial, bag, beaker, syringe, or the like. The container is then mixed by stirring, shaking, swirling, agitation, inversion or a combination thereof. In certain instances, a fractional volume of the liquid vehicle (i.e., one-half, one-third, one-fourth volume, etc.) is added to a enalapril powder formulation in a container, mixed by stirring, shaking, swirling, agitation, inversion or a combination thereof and the subsequent liquid fraction(s) is added and mixed. In certain instances, a one-half fractional volume of the liquid vehicle is added to an enalapril powder formulation in a container and mixing by shaking; the other one-half fractional volume of the

liquid vehicle is then subsequently added and mixed. In any of the above embodiments, mixing (i.e., stirring, shaking, swirling, agitation, inversion or a combination thereof) occurs for a certain time intervals such as about 10 seconds, about 20 seconds, about 30 seconds, about 45 seconds, about 60 seconds, about 90 seconds, about 120 seconds, about 2.5 minutes, about 3 minutes, about 3.5 minutes, about 4 minutes, or about 5 minutes. In embodiments, where there are two or more mixing steps, the time intervals for each mixing can be the same (e.g., 2×10 seconds) or different (e.g., 10 seconds for first mixing and 20 seconds for second mixing). In any of the above embodiments, a enalapril oral liquid formulation is allowed to stand for a period of time such as about 10 minutes, about 20 minutes, about 30 minutes, about 45 minutes, about 1 hour, about 1.5 hours or about 2 hours, to allow any air bubbles resultant from any of the mixing methods to dissipate.

Stability of Enalapril Powder Formulation

The enalapril powder formulations described herein are stable in various storage conditions including refrigerated, ambient and accelerated conditions. Stable as used herein refer to enalapril powder formulations having about 95% or greater of the initial enalapril amount and 5% w/w or less total impurities or related substances at the end of a given storage period. The percentage of impurities is calculated from the amount of impurities relative to the amount of enalapril. Stability is assessed by HPLC or any other known testing method. In some embodiments, the stable enalapril powder formulations have about 5% w/w, about 4% w/w, about 3% w/w, about 2.5% w/w, about 2% w/w, about 1.5% w/w, about 1% w/w, or about 0.5% w/w total impurities or related substances. In other embodiments, the stable enalapril powder formulations have about 5% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 4% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 3% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 2% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 1% w/w total impurities or related substances.

At refrigerated and ambient conditions, in some embodiments, the enalapril powder formulations described herein are stable for at least 1 week, 2 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 12 weeks, 16 weeks, 20 weeks, at least 24 weeks, at least 30 weeks, or at least 36 weeks. At accelerated conditions, in some embodiments, the enalapril powder formulations described herein are stable for at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks or at least 12 weeks. Accelerated conditions for the enalapril powder formulations described herein include temperature and/or relative humidity (RH) that are above ambient levels (e.g. 25±4° C.; 55±10% RH). In some instances, an accelerated condition is at about 30° C., about 35° C., about 40° C., about 45° C., about 50° C., about 55° C. or about 60° C. In other instances, an accelerated condition is above 65% RH, about 70% RH, about 75% RH or about 80% RH. In further instances, an accelerated condition is about 40° C. or 60° C. at ambient humidity. In yet further instances, an accelerated condition is about 40° C. at 75±5% RH humidity.

Kits and Articles of Manufacture

For the enalapril powder and liquid formulations described herein, kits and articles of manufacture are also described. Such kits can comprise a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method described herein including an enalapril powder or liquid formulation. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers can be formed from a variety of materials such as glass or plastic.

A kit will typically may comprise one or more additional containers, each with one or more of various materials (such as reagents, optionally in concentrated form, and/or devices) desirable from a commercial and user standpoint for an enalapril powder or liquid formulation described herein. Non-limiting examples of such materials include, but not limited to, buffers, diluents, filters, needles, syringes; carrier, package, container, vial and/or tube labels listing contents and/or instructions for use, and package inserts with instructions for use associated with an enalapril powder or liquid formulation. A set of instructions will also typically be included.

A label can be on or associated with the container. A label can be on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label can be associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. A label can be used to indicate that the contents are to be used for a specific therapeutic application. The label can also indicate directions for use of the contents, such as in the methods described herein.

Methods

Provided herein, in one aspect, are methods of treatment comprising administration of the enalapril oral liquid formulations described herein to a subject. In some embodiments, the enalapril oral liquid formulations described herein treat hypertension in a subject. Hypertension as used herein includes both primary (essential) hypertension and secondary hypertension. In certain instances, hypertension is classified in cases when blood pressure values are greater than or equal to 140/90 (systolic/diastolic) mm Hg in a subject. In certain instances, the enalapril oral liquid formulations described herein treat a subject having a blood pressure values are greater than or equal to 140/90 mm Hg. In certain instances, the enalapril oral liquid formulations described herein treat primary (essential) hypertension in a subject. In other instances, the enalapril oral liquid formulations described herein treat secondary hypertension in a subject.

In other embodiments, the enalapril oral liquid formulations described herein treat prehypertension in a subject. Prehypertension as used herein refers to cases where a subject's blood pressure is elevated above normal but not to the level considered to be hypertension. In some instances, prehypertension is classified in cases when blood pressure values are 120-139/80-89 mm Hg. In certain instances, the enalapril oral liquid formulations described herein treat a subject having blood pressure values of 120-139/80-89 mm Hg.

In yet other embodiments, the enalapril oral liquid formulations described herein are prophylactically administered to subjects suspected of having, predisposed to, or at risk of developing hypertension. In some embodiments, the administration of enalapril oral liquid formulations

described herein allow for early intervention prior to onset of hypertension. In certain embodiments, upon detection of a biomarker, environmental, genetic factor, or other marker, the enalapril oral liquid formulations described herein are prophylactically administered to subjects.

In further embodiments, the enalapril oral liquid formulations described herein treat heart failure (e.g., symptomatic congestive), asymptomatic left ventricular dysfunction, myocardial infarction, diabetic nephropathy and chronic renal failure. In certain instances, the enalapril oral liquid formulations described herein treat symptomatic congestive heart failure. In other instances, the enalapril oral liquid formulations described herein treat asymptomatic left ventricular dysfunction. In further instances, the enalapril oral liquid formulations described herein treat myocardial infarction. In yet further instances, the enalapril oral liquid formulations described herein treat diabetic nephropathy. In yet further instances, the enalapril oral liquid formulations described herein treat chronic renal failure.

Dosing

In one aspect, the enalapril oral liquid formulations are used for the treatment of diseases and conditions described herein. In addition, a method for treating any of the diseases or conditions described herein in a subject in need of such treatment, involves administration of enalapril oral liquid formulations in therapeutically effective amounts to said subject.

Dosages of enalapril oral liquid formulations described can be determined by any suitable method. Maximum tolerated doses (MTD) and maximum response doses (MRD) for enalapril and/or enalaprilat can be determined via established animal and human experimental protocols as well as in the examples described herein. For example, toxicity and therapeutic efficacy of enalapril and/or enalaprilat can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between the toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD_{50} and ED_{50}. Enalapril dosages exhibiting high therapeutic indices are of interest. The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED_{50} with minimal toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. Additional relative dosages, represented as a percent of maximal response or of maximum tolerated dose, are readily obtained via the protocols.

In some embodiments, the amount of a given enalapril oral liquid formulation that corresponds to such an amount varies depending upon factors such as the particular enalapril salt or form, disease condition and its severity, the identity (e.g., weight, sex) of the subject or host in need of treatment, but can nevertheless be determined according to the particular circumstances surrounding the case, including, e.g., the specific agent being administered, the liquid composition type, the condition being treated, and the subject or host being treated.

In some embodiments, the enalapril oral liquid formulations described herein are provided in a dose per day from about 0.01 mg to 100 mg, from about 0.1 mg to about 80 mg, from about 1 to about 60, from about 2 mg to about 40 mg of enalapril. In certain embodiments, the enalapril oral liquid formulations described herein are provided in a daily dose of about 0.01 mg, about 0.05 mg, about 0.1 mg, about 0.2 mg, about 0.4 mg, about 0.6 mg, about 0.8 mg, about 1 mg, about 1.5 mg, about 2 mg, about 2.5 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 76, mg, about 80 mg, about 85 mg, about 90 mg or about 100 mg, or any range derivable therein. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 1 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 2 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 3 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 4 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 5 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 6 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 7 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 8 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 9 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 10 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 11 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 12 mg. The dose per day described herein can be given once per day or multiple times per day in the form of sub-doses given b.i.d., t.i.d., q.i.d., or the like where the number of sub-doses equal the dose per day.

In further embodiments, the daily dosages appropriate for the enalapril oral liquid formulations described herein are from about 0.01 to about 1.0 mg/kg per body weight. In one embodiment, the daily dosages appropriate for the enalapril oral liquid formulations are from about 0.02 to about 0.8 mg/kg enalapril per body weight. In another embodiment, the daily dosage appropriate for the enalapril oral liquid formulations are from about 0.05 to about 0.6 mg/kg per body weight. In another embodiment, the daily dosage appropriate for the enalapril oral liquid formulations is about 0.05 mg/kg, about 0.06 mg/kg, about 0.07 mg/kg, about 0.08 mg/kg, about 0.10 mg/kg, about 0.15 mg/kg, about 0.20 mg/kg, about 0.25 mg/kg, about 0.30 mg/kg, about 0.40 mg/kg, about 0.50 mg/kg, or about 0.60 mg/kg.

In other embodiments the enalapril oral liquid formulations are provided at the maximum tolerated dose (MTD) for enalapril and/or enalaprilat. In other embodiments, the amount of the enalapril oral liquid formulations administered is from about 10% to about 90% of the maximum tolerated dose (MTD), from about 25% to about 75% of the MTD, or about 50% of the MTD. In particular embodiments, the amount of the enalapril oral liquid formulations administered is from about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or higher, or any range derivable therein, of the MTD for enalapril and/or enalaprilat.

In further embodiments, the enalapril oral liquid formulations are provided in a dosage that is similar, comparable

or equivalent to a dosage of a known enalapril tablet formulation. In other embodiments, the enalapril oral liquid formulations are provided in a dosage that provides a similar, comparable or equivalent pharmacokinetic parameters (e.g., AUC, C_{max}, T_{max}, C_{min}, $T_{1/2}$) as a dosage of a known enalapril tablet formulation. Similar, comparable or equivalent pharmacokinetic parameters, in some instances, refer to within 80% to 125%, 80% to 120%, 85% to 125%, 90% to 110%, or increments therein, of the given values. It should be recognized that the ranges can, but need not be symmetrical, e.g., 85% to 105%.

Administration

Administration of an enalapril oral liquid formulation is at a dosage described herein or at other dose levels and formulations determined and contemplated by a medical practitioner. In certain embodiments, the enalapril oral liquid formulations described herein are administered for prophylactic and/or therapeutic treatments. In certain therapeutic applications, the enalapril oral liquid formulations are administered to a patient already suffering from a disease, e.g., hypertension, in an amount sufficient to cure the disease or at least partially arrest or ameliorate the symptoms, e.g., lower blood pressure. Amounts effective for this use depend on the severity of the disease, previous therapy, the patient's health status, weight, and response to the enalapril formulations, and the judgment of the treating physician. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation clinical trial.

In prophylactic applications, the enalapril oral liquid formulations described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, e.g., hypertension. Such an amount is defined to be a "prophylactically effective amount or dose." In this use, the precise amounts also depend on the patient's state of health, weight, and the like. When used in a patient, effective amounts for this use will depend on the risk or susceptibility of developing the particular disease, previous therapy, the patient's health status and response to the enalapril formulations, and the judgment of the treating physician.

In certain embodiments wherein the patient's condition does not improve, upon the doctor's discretion the administration of an enalapril oral liquid formulations described herein are administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease. In other embodiments, administration of an enalapril oral liquid formulation continues until complete or partial response of a disease.

In certain embodiments wherein a patient's status does improve, the dose of an enalapril oral liquid formulation being administered may be temporarily reduced or temporarily suspended for a certain length of time (i.e., a "drug holiday"). In specific embodiments, the length of the drug holiday is between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, and 365 days. The dose reduction during a drug holiday is, by way of example only, by 10%-100%, including by way of example only 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 100%.

In some embodiments, enalapril oral liquid formulations described herein are administered chronically. For example, in some embodiments, an enalapril oral liquid formulation is administered as a continuous dose, i.e., administered daily to a subject. In some other embodiments, enalapril oral liquid formulations described herein are administered intermittently (e.g. drug holiday that includes a period of time in which the formulation is not administered or is administered in a reduced amount).

In some embodiments an enalapril oral liquid formulation is administered to a subject who is in a fasted state. A fasted state refers to a subject who has gone without food or fasted for a certain period of time. General fasting periods include at least 4 hours, at least 6 hours, at least 8 hours, at least 10 hours, at least 12 hours, at least 14 hours and at least 16 hours without food. In some embodiments, an enalapril oral liquid formulation is administered orally to a subject who is in a fasted state for at least 8 hours. In other embodiments, an enalapril oral liquid formulation is administered to a subject who is in a fasted state for at least 10 hours. In yet other embodiments, an enalapril oral liquid formulation is administered to a subject who is in a fasted state for at least 12 hours. In other embodiments, an enalapril oral liquid formulation is administered to a subject who has fasted overnight.

In other embodiments an enalapril oral liquid formulation is administered to a subject who is in a fed state. A fed state refers to a subject who has taken food or has had a meal. In certain embodiments, an enalapril oral liquid formulation is administered to a subject in a fed state 5 minutes post-meal, 10 minutes post-meal, 15 minutes post-meal, 20 minutes post-meal, 30 minutes post-meal, 40 minutes post-meal, 50 minutes post-meal, 1 hour post-meal, or 2 hours post-meal. In certain instances, an enalapril oral liquid formulation is administered to a subject in a fed state 30 minutes post-meal. In other instances, an enalapril oral liquid formulation is administered to a subject in a fed state 1 hour post-meal. In yet further embodiments, an enalapril oral liquid formulation is administered to a subject with food.

In further embodiments described herein, an enalapril oral liquid formulation is administered at a certain time of day for the entire administration period. For example, an enalapril oral liquid formulation can be administered at a certain time in the morning, in the evening, or prior to bed. In certain instances, an enalapril oral liquid formulation is administered in the morning. In other embodiments, an enalapril oral liquid formulation can be administered at different times of the day for the entire administration period. For example, an enalapril oral liquid formulation can be administered on 8:00 am in the morning for the first day, 12 pm noon for the next day or administration, 4 pm in the afternoon for the third day or administration, and so on.

Further Combinations

The treatment of certain diseases or conditions (e.g., hypertension, heart failure, myocardial infarction and the like) in a subject with an enalapril oral liquid formulation described herein encompass additional therapies and treatment regimens with other agents in some embodiments. Such additional therapies and treatment regimens can include another therapy, e.g., additional anti-hypertensives, for treatment of the particular disease or condition in some embodiments. Alternatively, in other embodiments, additional therapies and treatment regimens include other agents used to treat adjunct conditions associated with the disease or condition or a side effect from the enalapril oral liquid formulation in the therapy.

Additional agents for use in combination with an enalapril oral liquid formulation described herein include, but are not limited to, diuretics (loop, thiazide, potassium-sparing, and the like), beta blockers (metoprolol, propanolol, pronethalol,

and the like), alpha blockers (phentolamine, phenoxybenzamine, tamsulosin, prazosin, and the like), mixed alpha and beta blockers (bucindolol, carvedilol, labetalol), calcium channel blockers (dihydropyridines such as nifedipine, amlodipine, etc., dilitazem, verapamil and the like), angiotensin II receptor antagonists (saralasin, lsartan, eprosartin, irbesartan, valsartan, and the like), other ACE inhibitors (captopril, quinapril, ramipril, lisinopril, zofenopril, and the like), aldosterone antagonists (eplerenone, spironolactone and the like), vasodilators (hydralazine and the like) and alpha-2 agonists (clonidine, moxonidine, guanabenz and the like).

Certain Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments described herein, certain preferred methods, devices, and materials are now described.

As used herein and in the appended claims, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to "an excipient" is a reference to one or more excipients and equivalents thereof known to those skilled in the art, and so forth.

The term "about" is used to indicate that a value includes the standard level of error for the device or method being employed to determine the value. The use of the term "or" in the claims is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and to "and/or." The terms "comprise," "have" and "include" are open-ended linking verbs. Any forms or tenses of one or more of these verbs, such as "comprises," "comprising," "has," "having," "includes" and "including," are also open-ended. For example, any method that "comprises," "has" or "includes" one or more steps is not limited to possessing only those one or more steps and also covers other unlisted steps.

"Optional" or "optionally" may be taken to mean that the subsequently described structure, event or circumstance may or may not occur, and that the description includes instances where the events occurs and instances where it does not.

As used herein, the term "therapeutic" means an agent utilized to treat, combat, ameliorate, prevent or improve an unwanted condition or disease of a patient. In some embodiments, a therapeutic agent such as enalapril is directed to the treatment and/or the amelioration of, reversal of, or stabilization of the symptoms of hypertension described herein.

"Administering" when used in conjunction with a therapeutic means to administer a therapeutic systemically or locally, as directly into or onto a target tissue, or to administer a therapeutic to a patient whereby the therapeutic positively impacts the tissue to which it is targeted. Thus, as used herein, the term "administering", when used in conjunction with an enalapril formulation, can include, but is not limited to, providing an enalapril formulation into or onto the target tissue; providing an enalapril formulation systemically to a patient by, e.g., oral administration whereby the therapeutic reaches the target tissue or cells. "Administering" a formulation may be accomplished by injection, topical administration, and oral administration or by other methods alone or in combination with other known techniques.

The term "animal" as used herein includes, but is not limited to, humans and non-human vertebrates such as wild, domestic and farm animals. As used herein, the terms "patient," "subject" and "individual" are intended to include living organisms in which certain conditions as described herein can occur. Examples include humans, monkeys, cows, sheep, goats, dogs, cats, mice, rats, and transgenic species thereof. In a preferred embodiment, the patient is a primate. In certain embodiments, the primate or subject is a human. In certain instances, the human is an adult. In certain instances, the human is child. In further instances, the human is 12 years of age or younger. In certain instances, the human is elderly. In other instances, the human is 60 years of age or older. Other examples of subjects include experimental animals such as mice, rats, dogs, cats, goats, sheep, pigs, and cows. The experimental animal can be an animal model for a disorder, e.g., a transgenic mouse with hypertensive pathology. A patient can be a human suffering from hypertension, or its variants or etiological forms.

By "pharmaceutically acceptable", it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The term "pharmaceutical composition" shall mean a composition comprising at least one active ingredient, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

A "therapeutically effective amount" or "effective amount" as used herein refers to the amount of active compound or pharmaceutical agent that elicits a biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following: (1) preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease, (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology), and (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology). As such, a non-limiting example of a "therapeutically effective amount" or "effective amount" of a formulation of the present disclosure may be used to inhibit, block, or reverse the activation, migration, or proliferation of cells or to effectively treat hypertension or ameliorate the symptoms of hypertension.

The terms "treat," "treated," "treatment," or "treating" as used herein refers to both therapeutic treatment in some embodiments and prophylactic or preventative measures in other embodiments, wherein the object is to prevent or slow (lessen) an undesired physiological condition, disorder or disease, or to obtain beneficial or desired clinical results. For the purposes described herein, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of the condition, disorder or disease; stabilization (i.e., not worsening) of the state of the condition, disorder or disease; delay in onset or slowing of the progression of the condition, disorder or disease;

amelioration of the condition, disorder or disease state; and remission (whether partial or total), whether detectable or undetectable, or enhancement or improvement of the condition, disorder or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment. A prophylactic benefit of treatment includes prevention of a condition, retarding the progress of a condition, stabilization of a condition, or decreasing the likelihood of occurrence of a condition. As used herein, "treat," "treated," "treatment," or "treating" includes prophylaxis in some embodiments.

EXAMPLES

Example A: Effect of pH on the Formation of Degradants in Enalapril Formulations at 60° C.

Formulations were prepared containing enalapril maleate according to Table A-1. The pH of each solution was recorded. Five milliliters of each formulation were transferred to each of four 3-dram glass screw-capped vials with Teflon inserts in the caps. The vials were placed into a 60° C. heating chamber then one vial removed and analyzed by HPLC at times of zero, ~97 and ~180 hours.

TABLE A-1

Formulation (in mg/mL) of Enalapril Formulations at Varying pH and Citrate Buffer Concentration

	Formulation (mM citrate)					
Component	A1 (50)	A2 (50)	A3 (50)	A4 (50)	A5 (50)	A6 (25)
Enalapril maleate	1.0	1.0	1.0	1.0	1.0	1.0
Mannitol	50	50	50		50	6.0
Xylitol				50		
Citric acid, anhydrous	7.35	5.05	2.55	5.05	5.05	2.76
Sodium citrate, dihydrate	3.45	7.0	10.8	7.0	7.0	3.15
Sodium benzoate	1	1	1	1	1	
Methylparaben sodium					1.75	0.335
Propylparaben sodium						0.095
Potassium sorbate						1
Sucralose	0.75	0.75	0.75	0.75	0.75	0.75
Silicon dioxide						0.075
Mixed berry flavor (powdered)	0.5	0.5	0.5	0.5	0.5	0.5
Water	qs	qs	qs	qs	qs	qs
pH	3.4	4.4	5.2	4.4	4.5	4.4

qs = sufficient quantity

The results of the HPLC analysis for the two main degradants in the samples, enalapril diketopiperazine and enalaprilat, are provided in Table A-2.

TABLE A-2

Primary Degradants Present in the Formulations (% w/w of enalapril maleate)

	Formulation					
Hours at 60° C.	A1	A2	A3	A4	A5	A6
Enalapril Diketopiperazine						
0	0.04	0.03	0.03	0.03	0.03	0.03
97	3.10	0.88	0.33	0.86	0.70	0.53
180	6.21	1.77	0.75	1.73	1.43	1.07

TABLE A-2-continued

Primary Degradants Present in the Formulations (% w/w of enalapril maleate)

	Formulation					
Hours at 60° C.	A1	A2	A3	A4	A5	A6
Enalaprilat						
0	0.09	0.15	0.29	0.14	0.16	0.12
97	5.20	16.9	47.4	16.1	20.3	15.6
180	9.94	34.8	113	33.5	42.2	31.7

Example B: Effect of Buffer Concentration on the Formation of Degradants in Enalapril Formulations at 60° C.

Formulations were prepared containing enalapril maleate according to Table B-1. The pH of each solution was measured and adjusted as needed to pH 3.3 with ~1N HCl or ~0.5N NaOH. Five milliliters of each formulation were transferred to each of six 3-dram glass screw-capped vials with Teflon inserts in the caps. The vials were placed into a 60° C. heating chamber then two vials were removed and analyzed by HPLC at times of zero, ~66 and ~139 hours.

TABLE B-1

Formulation (in mg/mL) of Enalapril Maleate Formulations at Varying Citrate Buffer Concentrations

	Formulation		
Component	B1 (5 mM citrate)	B2 (10 mM citrate)	B3 (20 mM citrate)
Enalapril maleate	1.0	1.0	1.0
Citric acid, anhydrous	0.82	1.65	3.29
Sodium citrate, anhydrous	0.19	0.38	0.75
Sodium benzoate	1.0	1.0	1.0
Sucralose	0.7	0.7	0.7
Mixed berry flavor (powdered)	0.5	0.5	0.5
Water	qs	qs	qs
pH	3.3	3.3	3.3

qs = sufficient quantity

The results of the HPLC analysis for the two main degradants in the samples, enalapril diketopiperazine and enalaprilat, are provided in Table B-2.

TABLE B-2

Primary Degradants Present in the Formulations (% w/w of enalapril maleate)

Hours at 60° C.	Formulation B1 (5 mM citrate)	B2 (10 mM citrate)	B3 (20 mM citrate)
Enalapril Diketopiperazine			
0	0.01	0.01	0.01
66	1.57	1.63	1.79
139	3.70	3.94	4.24
Enalaprilat			
0	0.00	0.00	0.00
66	2.98	2.88	3.19
139	5.28	5.23	5.69

Example C: Stability of Enalapril Maleate Formulations Containing Paraben Preservatives

Powder formulations were prepared according to Table C-1. All components in each formulation except mannitol or xylitol were added to a 2.5 liter polypropylene screw capped bottle. The bottle was mixed by inversion in a Turbula® mixer for 5 minutes. The mannitol or xylitol was then added and the components mixed for 5 minutes, then the other half of the mannitol or xylitol was added and a final mix of 5 minutes was completed.

One liter of solution formulation was prepared for each formulation by adding an appropriate amount of each powdered formulation to a 1 liter volumetric flask and adding about 500 mL water. The powder was dissolved with mixing then the contents of the flask were brought to 1 liter with additional water. The amount of powder to add was determined such that the final concentration of enalapril maleate was 1.0 mg/mL. Fifty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5° C.±3° C., at room temperature (19-23° C.) and at 40° C.±2° C. At various times, bottles were removed from the storage condition and analyzed.

TABLE C-1

Composition of Enalapril Maleate Formulations

	Component C1	C2	C3	C4	C5
Powder Formulation (grams)					
Enalapril maleate	12.3	12.3	8.86	2.16	2.16
Mannitol	74.4	74.4	394.0		
Xylitol				96.6	93.7
Citric acid, anhydrous	28.6	35.6	28.4	5.40	5.40
Sodium citrate, anhydrous	24.5	14.7	7.73	4.10	4.10
Sodium methylparaben	4.17	4.17	8.86	2.16	2.16
Sodium propylparaben	1.10	1.10			
Potassium sorbate	12.3	12.3			
Sodium benzoate			8.86	2.16	2.16
Xanthan Gum					1.62
Colloidal silicon dioxide	0.859	0.859	4.43		1.08
Sucralose	9.20	9.20	6.64	1.62	1.62
Mixed berry flavor	6.13	6.13	4.43	1.08	1.08
Total solids	173.5	170.7	472.3	115.2	115.2
Liquid Formulations (mg/mL)					
Enalapril maleate	1.00	1.00	1.00	1.00	1.00
Mannitol	6.07	6.07	44.5		
Xylitol				44.7	43.4
Citric acid, anhydrous	2.33	2.90	3.21	2.50	2.50
Sodium citrate, anhydrous	2.00	1.20	0.87	1.90	1.90
Sodium methylparaben	0.34	0.34	1.00	1.00	1.00
Sodium propylparaben	0.09	0.09	1.00		
Potassium sorbate	1.00	1.00			
Sodium benzoate			1.00	1.00	1.00
Xanthan Gum					0.75
Colloidal silicon dioxide	0.07	0.07	0.50		0.50
Sucralose	0.75	0.75	0.75	0.75	0.75
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50
pH (measured)	4.4	3.8	3.7	4.4	4.6

The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table C-2.

TABLE C-2

Degradant Content After Storage (% w/w of enalapril maleate)

	Storage ° C.	Weeks	Formulation C1	C2	C3	C4	C5
			Liquid Formulations				
Diketo-piperazine	5	0	0.03	0.04	0.04	0.02	0.02
		4	0.02	0.03	0.03	0.03	0.02
		8	0.03	0.04	0.04		
	19-23	0	0.03	0.04	0.04	0.02	0.02
		4	0.05	0.09	0.11	0.05	0.04
		8	0.08	0.17	0.19		
	40	0	0.03	0.04	0.04	0.02	0.02
		4	0.35	0.91	1.10	0.31	0.21
		8	0.65	1.80	2.05		
Enalaprilat	5	0	0.18	0.14	0.12	0.13	0.19
		4	0.18	0.15	0.12	0.43	0.53
		8	0.55	0.38	0.34		
	19-23	0	0.18	0.14	0.12	0.13	0.19
		4	1.35	0.83	0.80	1.75	2.29
		8	3.34	2.06	1.98		
	40	0	0.18	0.14	0.12	0.13	0.19
		4	10.49	6.08	6.11	12.30	16.14
		8	24.37	14.12	14.22		

Example D: Stability of Enalapril Maleate Formulations Containing Benzoate Preservative

Powder formulations were prepared according to Table D-1. All components in each formulation except enalapril maleate and mannitol or xylitol were blended with a mortar and pestle. The enalapril maleate was then triturated with the blend. The xylitol or mannitol was then triturated into the blend using a geometric dilution technique.

One liter of solution formulation was prepared for each formulation by adding an appropriate amount of each powdered formulation to a 1 liter volumetric flask and adding about 500 mL water. The powder was dissolved with mixing then the contents of the flask were brought to 1 liter with additional water. The amount of powder to add was determined such that the final concentration of enalapril maleate

was 1.0 mg/mL. Fifty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5° C.±3° C., at room temperature (19-23° C.) and at 40° C.±2° C. At various times, bottles were removed from the storage condition and analyzed.

TABLE D-1

Composition of Enalapril Maleate Formulations

Component	D1	D2	D3	D4	D5	D6
Powder Formulation (grams)						
Enalapril maleate	3.63	3.63	3.63	3.63	8.86	2.16
Xylitol	537.2	176.1		537.2		
Mannitol			319.4		401.2	98.9
Citric acid, anhydrous	11.9	11.9	11.9	10.4	26.6	6.48
Sodium citrate, anhydrous	2.72	2.72	2.72	4.86	11.3	2.76
Sodium benzoate	3.63	3.63	3.63	3.63	8.86	2.16
Rebalance X60 (sucralose and maltodextrin)		10.9				
Sucralose					6.64	1.62
Saccharin sodium			7.26			
Colloidal silicon dioxide					4.43	
Mixed berry flavor	1.82	1.82	1.82	1.82	4.43	1.08
Total solids	561	211	350.	561	472.3	115.2
Liquid Formulations (mg/mL)						
Enalapril maleate	1.00	1.00	1.00	1.00	1.00	1.00
Xylitol	148.0	48.5		148.0		
Mannitol			88.0		45.3	45.8
Citric acid, anhydrous	3.29	3.29	3.29	2.85	3.00	3.00
Sodium citrate, anhydrous	0.75	0.75	0.75	1.34	1.28	1.28
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00
Rebalance X60 (sucralose and maltodextrin)		3.00				
Sucralose					0.75	0.75
Saccharin sodium			2.00			
Colloidal silicon dioxide					0.50	
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50	0.50
pH (measured)	3.2	3.2	3.4	3.7	3.6	3.6

The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table D-2.

TABLE D-2

Degradant Content After Storage (% w/w of enalapril maleate)

	Storage		Formulation					
	° C.	Weeks	D1	D2	D3	D4	D5	D6
			Liquid Formulations					
Diketo-piperazine	5	0	0.04	0.02	0.03	0.03	0.04	0.04
		4	0.07	0.03	0.05	0.05	0.03	
		8	0.11	0.06	0.08	0.08	0.05	
		12	0.08	0.04	0.06	0.06		
		26	0.11	0.07	0.09	0.07		
	19-23	0	0.04	0.02	0.03	0.03	0.04	0.04
		4	0.27	0.21	0.24	0.16	0.12	0.12
		8	0.50	0.41	0.47	0.30	0.21	0.22
		12	0.62	0.52	0.58	0.35		
		26	1.39	1.20	1.33	0.76		

TABLE D-2-continued

Degradant Content After Storage (% w/w of enalapril maleate)

	Storage		Formulation					
	° C.	Weeks	D1	D2	D3	D4	D5	D6
			Liquid Formulations					
	40	0	0.04	0.02	0.03	0.03	0.04	0.04
		4	2.87	2.32	2.73	1.57	1.21	1.13
		8	5.13	4.42	5.44	2.97	2.23	2.16
		12	6.86	5.90	6.90	3.91		
		26	13.63	12.18	13.56	7.74		
Enalaprilat	5	0	0.03	0.02	0.03	0.03	0.13	0.14
		4	0.15	0.12	0.06	0.17	0.13	
		8	0.22	0.19	0.22	0.27	0.34	
		12	0.20	0.17	0.19	0.22		
		8	0.32	0.30	0.30	0.39		
	19-23	0	0.03	0.02	0.03	0.03	0.13	0.14
		4	0.69	0.66	0.69	0.86	0.74	0.76
		8	1.38	1.33	1.41	1.68	1.83	1.82
		12	1.71	1.68	1.73	2.15		
		26	3.63	3.61	3.59	4.55		
	40	0	0.03	0.02	0.03	0.03	0.13	0.14
		4	4.76	4.42	4.76	6.45	5.55	5.24
		8	8.95	8.64	9.61	12.94	12.73	12.18
		12	11.01	10.64	11.41	16.16		
		26	17.18	17.11	18.30	27.36		

Example E: Stability of Solution Formulations of Enalapril Maleate

Solution formulations were prepared according to Table E-1. Thirty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5° C.±3° C., at room temperature (19-23° C.) and at 40° C.±2° C. At various times, bottles were removed from the storage condition and analyzed.

Composition of Enalapril Maleate Formulations (mg/mL)

Component	E1	E2	E3	E4	E5	E6
Enalapril maleate	1.00	1.00	1.00	1.00	1.00	1.00
Xylitol	150	200		150		
Citric acid anhydrous	3.29	3.29	3.29	3.29	1.65	0.82
Sodium citrate anhydrous	0.75	0.75	0.75	0.75	0.38	0.19
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00
Sucralose			0.70		0.70	0.70
Mixed berry flavor	0.50		0.50	0.50	0.50	0.50
Water	qs	qs	qs	qs	qs	qs
pH (measured)	3.3	3.3	3.3	3.4	3.3	3.3

qs = sufficient quantity

The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table E-2.

TABLE E-2

Degradant Content After Storage (% w/w of enalapril maleate)

	Storage		Formulation					
	° C.	Weeks	E1	E2	E3	E4	E5	E6
Diketo-piperazine	5	0	0.01	0.01	0.01	0.01	0.01	0.01
		4	0.04	0.04	0.05	0.04	0.03	0.03
		8	0.04	0.04	0.04	0.04	0.03	0.03
		12	0.05	0.05	0.04	0.05	0.04	0.04
		26	0.07	0.06	0.05	0.06	0.05	0.05
		52					0.15	0.14
		62	0.18	0.18	0.16	0.14		

TABLE E-2-continued

Degradant Content After Storage (% w/w of enalapril maleate)

	Storage		Formulation					
	° C.	Weeks	E1	E2	E3	E4	E5	E6
	19-23	0	0.01	0.01	0.01	0.01	0.01	0.01
		4	0.22	0.23	0.21	0.20	0.16	0.15
		8	0.35	0.35	0.32	0.31	0.29	0.28
		12	0.58	0.59	0.53	0.51	0.48	0.45
		26	1.10	1.10	1.00	0.95	0.97	0.92
		52					2.30	2.15
		62	3.02	3.04	2.75	2.64		
	40	0	0.01	0.01	0.01	0.01	0.01	0.01
		4	2.65	2.71	2.60	2.42	1.76	1.68
		8	4.02	3.99	3.99	3.62	3.37	3.13
		12	6.72	6.42	6.47	6.00	5.53	5.29
Enalaprilat	5	0	0.00	0.00	0.01	0.02	0.00	0.00
		4	0.07	0.09	0.10	0.11	0.07	0.08
		8	0.12	0.14	0.10	0.13	0.09	0.08
		12	0.16	0.15	0.15	0.17	0.14	0.11
		26	0.31	0.30	0.29	0.31	0.27	0.24
		52					0.54	0.46
		62	0.75	0.75	0.74	0.71		
	19-23	0	0.00	0.00	0.01	0.02	0.00	0.00
		4	0.65	0.65	0.68	0.70	0.50	0.46
		8	1.17	1.19	1.20	1.23	1.03	0.95
		12	1.67	1.69	1.72	1.80	1.30	1.21
		26	3.36	3.38	3.42	3.57	3.07	2.90
		52					6.32	5.88
		62	7.99	8.02	8.04	8.57		
	40	0	0.00	0.00	0.01	0.02	0.00	0.00
		4	4.85	4.93	5.19	5.42	3.33	3.25
		8	8.08	8.06	8.56	9.01	6.65	6.35
		12	10.70	10.48	11.01	11.97	8.14	7.96

Example F: Effect of pH on the Formation of Degradants in Enalapril Formulations at 5° C. and 19-23° C.

The content of enalapril diketopiperazine and enalaprilat that were formed after 8 weeks of storage for formulations C1-C3 and D1-D5 are plotted in FIG. **1** (5° C.±3° C.) and FIG. **2** (19-23° C. storage). These formulations all contained 20 mM total citrate buffer content, but with varying pH. The general effects of formulation pH on the formation of the two main enalapril degradants are shown.

Example G: Antimicrobial Effectiveness Testing of Enalapril Maleate Formulations at pH 3.3

Enalapril formulations were prepared containing differing amounts of the antimicrobial preservative, sodium benzoate. The formulations were then tested for antimicrobial effectiveness (AET) according to the procedures in the 2014 United States Pharmacopeia 37, Chapter <51> for category 3 products. The formulation of the formulations and the AET results are included in Table G-1.

TABLE G-1

Formulation and AET Testing Results

	Formulation				
	G1	G2	G3	G4	G5
Formulation (mg/mL)					
Enalapril maleate	1.00	1.00	1.00	1.00	1.00
Xylitol	150	150	150	150	
Sucralose					0.70
Citric acid, anhydrous	1.64	1.64	1.64	1.64	1.80
Sodium citrate, anhydrous	0.322	0.322	0.322	0.322	
Sodium citrate, dihydrate					0.165
Sodium benzoate	1.00	0.80	0.60	0.40	1.0
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50
Water	q.s.	q.s.	q.s.	q.s.	q.s.
HCl/NaOH	as need to achieve pH				
Measured pH	3.3	3.3	3.3	3.3	3.3
AET Results					
USP <51>	Pass	Pass	Pass	Pass	Pass

qs = sufficient quantity

Example H: Clinical Trial: Bioavailability Study of 10 mg Enalapril Maleate Oral Solution vs. 10 mg Epaned® Powder for Oral Solution (Reconstituted) Under Fasted Conditions

The objective of this open-label, randomized, two-period, two-treatment, two-way crossover study was to compare the oral bioavailability of a test formulation of 10 mL of enalapril maleate oral solution, 1 mg/mL (formulation E-5), to an equivalent oral dose of the commercially available comparator product, Epaned® (enalapril maleate) Powder for Oral Solution, 1 mg/mL, when administered under fasted conditions in healthy adults.

Study design: Thirty-two healthy adult subjects received a single 10 mL dose of enalapril maleate oral solution, 1 mg/mL, formulation E-5 (Treatment A), in one period and a separate single dose of Epaned Powder for Oral Solution (reconstituted with the supplied Ora-Sweet SF), 1 mg/mL (Treatment B) in another period. Each treatment was administered after an overnight fast of at least 10 hours, followed by a 4-hour fast postdose. Each treatment was administered via a 10 mL oral dosing syringe and followed with 240 mL of room temperature tap water. Each drug administration was separated by a washout period of at least 7 days.

During each study period, meals were the same and scheduled at approximately the same times relative to dose. In addition, during each period, blood samples were obtained prior to and following each dose at selected times through 72 hours postdose. Pharmacokinetic samples were analyzed for enalapril and its metabolite enalaprilat using a validated analytical method; appropriate pharmacokinetic parameters were calculated for each formulation using non-compartmental methods. Blood was also drawn and urine collected for clinical laboratory testing at screening and at the end of the study.

Statistical Methods: The concentration-time data were analyzed using noncompartmental methods in Phoenix™ WinNonlin® (Version 6.3, Pharsight Corporation). Concentration-time data that were below the limit of quantitation (BLQ) were treated as zero in the data summarization and descriptive statistics. In the pharmacokinetic analysis, BLQ concentrations were treated as zero from time-zero up to the time at which the first quantifiable concentration was observed; embedded and/or terminal BLQ concentrations were treated as "missing". Actual sample times were used for all pharmacokinetic and statistical analyses. Analysis of variance (ANOVA) and the Schuirmann's two one-sided t-test procedures at the 5% significance level were applied to

the log-transformed pharmacokinetic exposure parameters, C_{max}, AUC_{last}, and AUC_{inf}. The 90% confidence interval for the ratio of the geometric means (Test/Reference) was calculated. Bioequivalence was declared if the lower and upper confidence intervals (CIs) of the log-transformed parameters were within 80% to 125% for enalapril and enalaprilat.

Results: A total of 32 subjects participated in the study and 29 of these subjects completed both study periods. Based on the geometric mean ratios of enalapril and enalaprilat AUCs (AUC_{last} and AUC_{inf}), the bioavailability of the enalapril maleate oral solution (formulation E-5) relative to the Epaned Powder for Oral Solution (reconstituted) was approximately 105% to 110%. The geometric mean ratios of enalapril and enalaprilat C_{max} were approximately 115% and 109%, respectively. The 90% CI for comparing the maximum exposure to enalapril and enalaprilat, based on ln (C_{max}), was within the accepted 80% to 125% limits. The 90% CIs for comparing total systemic exposure to enalapril and enalaprilat, based on ln (AUG_{last}) and ln (AUC_{inf}), was within the accepted 80% to 125% limits. Therefore, the test formulation of enalapril maleate oral solution, 1 mg/mL, is bioequivalent to the reference product, Epaned Powder for Oral Solution (reconstituted), 1 mg/mL, under fasted conditions.

While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

What is claimed is:

1. A stable oral liquid formulation, consisting essentially of:

(i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;

(ii) a preservative, wherein the preservative is sodium benzoate, ascorbic acid, ascorbyl palmitate, BHA, BHT, EDTA and its salts, erythorbic acid, fumaric acid, malic acid, propyl gallate, sodium ascorbate, sodium bisulfate, sodium metabisulfite, sodium sulfite, benzoic acid, potassium sorbate, vanillin, a paraben, or a mixture of parabens; and

(iii) water;

wherein the formulation optionally comprises a buffer to maintain the pH about 4.5 or below, a sweetener, a flavoring agent, or any combination thereof;

wherein the formulation is stable at about 5±3° C. for at least 12 months; and

wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

2. The stable oral liquid formulation of claim **1**, comprising a sweetener.

3. The stable oral liquid formulation of claim **1**, comprising a buffer, wherein the buffer comprises a citrate, a phosphate, a citrate/phosphate, an acetate, a glycinate, an amino acid, or a tartrate buffer.

4. The stable oral liquid formulation of claim **3**, wherein the buffer is present at a concentration of about 10 mM to about 20 mM.

5. The stable oral liquid formulation of claim **3**, wherein the buffer maintains the pH between about 3 and about 4.

6. The stable oral liquid formulation of claim **1**, comprising about 1.0 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof.

7. The stable oral liquid formulation of claim **1**, wherein the enalapril or a pharmaceutically acceptable salt or solvate thereof is enalapril maleate.

8. The stable oral liquid formulation of claim **1**, wherein the preservative is sodium benzoate, ascorbic acid, ascorbyl palmitate, BHA, BHT, EDTA and its salts, erythorbic acid, fumaric acid, malic acid, propyl gallate, sodium ascorbate, sodium bisulfate, sodium metabisulfite, sodium sulfite, benzoic acid, potassium sorbate, or vanillin.

9. The stable oral liquid formulation of claim **1**, wherein the preservative is sodium benzoate.

10. The stable oral liquid formulation of claim **1**, wherein the preservative is present at about 0.1 mg/ml to about 2 mg/ml in the oral liquid formulation.

11. The stable oral liquid formulation of claim **1**, wherein the preservative is present at about 0.1 mg/ml to about 0.5 mg/ml in the oral liquid formulation.

12. The stable oral liquid formulation of claim **1**, wherein the formulation is stable at about 5±3° C. for at least 18 months.

13. A stable oral liquid formulation, consisting essentially of:

(i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;

(ii) a preservative, wherein the preservative is sodium benzoate, ascorbic acid, ascorbyl palmitate, BHA, BHT, EDTA and its salts, erythorbic acid, fumaric acid, malic acid, propyl gallate, sodium ascorbate, sodium bisulfate, sodium metabisulfite, sodium sulfite, benzoic acid, potassium sorbate, vanillin, a paraben, or a mixture of parabens; and

(iii) water;

wherein the formulation optionally comprises a buffer that is present in the formulation at a concentration of up to 20 mM, a sweetener, a flavoring agent, or any combination thereof;

wherein the formulation is stable at about 5±3° C. for at least 12 months; and

wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

14. The stable oral liquid formulation of claim **13**, comprising a sweetener.

15. The stable oral liquid formulation of claim **13**, comprising a buffer, wherein the buffer comprises a citrate, a phosphate, a citrate/phosphate, an acetate, a glycinate, an amino acid, or a tartrate buffer.

16. The stable oral liquid formulation of claim **15**, wherein the buffer maintains the pH about 4.5 or below.

17. The stable oral liquid formulation of claim **13**, wherein the enalapril or a pharmaceutically acceptable salt or solvate thereof is enalapril maleate.

18. The stable oral liquid formulation of claim **13**, wherein the preservative is sodium benzoate.

19. The stable oral liquid formulation of claim **13**, wherein the preservative is paraben or a mixture of parabens.

20. The stable oral liquid formulation of claim **13**, wherein the preservative is present at about 0.1 mg/ml to about 2 mg/ml in the oral liquid formulation.

21. The stable oral liquid formulation of claim **15**, wherein the buffer is present in the formulation at a concentration of about 5 mM, about 6 mM, about 7 mM, about 8 mM, about 9 mM, about 10 mM, about 11 mM, about 12 mM, about 13 mM, about 14 mM, about 15 mM, about 16 mM, about 17 mM, about 18 mM, about 19 mM, or about 20 mM.

22. The stable oral liquid formulation of claim **13**, wherein the formulation is stable at about 5±3° C. for at least 18 months.

23. The stable oral liquid formulation of claim **3**, wherein the buffer is present at a concentration of about 5 mM to about 20 mM.

* * * * *

JS 44 (Rev. 04/21)

CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. *(SEE INSTRUCTIONS ON NEXT PAGE OF THIS FORM.)*

I. (a) PLAINTIFFS
AZURITY PHARMACEUTICALS, INC.

(b) County of Residence of First Listed Plaintiff _____
(EXCEPT IN U.S. PLAINTIFF CASES)

(c) Attorneys *(Firm Name, Address, and Telephone Number)*
Woodrow Pollack, Shutts & Bowen, 4301 W. Boy Scout Blvd, #300, Tampa, FL 33607 (813) 463-4894

DEFENDANTS
CORERX, INC.

County of Residence of First Listed Defendant Pinellas
(IN U.S. PLAINTIFF CASES ONLY)
NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF LAND INVOLVED.

Attorneys *(If Known)*

II. BASIS OF JURISDICTION *(Place an "X" in One Box Only)*

- ☐ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question *(U.S. Government Not a Party)*
- ☐ 2 U.S. Government Defendant
- ☐ 4 Diversity *(Indicate Citizenship of Parties in Item III)*

III. CITIZENSHIP OF PRINCIPAL PARTIES *(Place an "X" in One Box for Plaintiff and One Box for Defendant)*
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Citizen of Another State	☐ 2	☐ 2	Incorporated *and* Principal Place of Business In Another State	☐ 5	☐ 5
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- ☐ 151 Medicare Act
- ☐ 152 Recovery of Defaulted Student Loans (Excludes Veterans)
- ☐ 153 Recovery of Overpayment of Veteran's Benefits
- ☐ 160 Stockholders' Suits
- ☐ 190 Other Contract
- ☐ 195 Contract Product Liability
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- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent Lease & Ejectment
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

TORTS

PERSONAL INJURY
- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault, Libel & Slander
- ☐ 330 Federal Employers' Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury
- ☐ 362 Personal Injury - Medical Malpractice

PERSONAL INJURY
- ☐ 365 Personal Injury - Product Liability
- ☐ 367 Health Care/ Pharmaceutical Personal Injury Product Liability
- ☐ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ☐ 370 Other Fraud
- ☐ 371 Truth in Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

CIVIL RIGHTS
- ☐ 440 Other Civil Rights
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 445 Amer. w/Disabilities - Employment
- ☐ 446 Amer. w/Disabilities - Other
- ☐ 448 Education

PRISONER PETITIONS

Habeas Corpus:
- ☐ 463 Alien Detainee
- ☐ 510 Motions to Vacate Sentence
- ☐ 530 General
- ☐ 535 Death Penalty

Other:
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition
- ☐ 560 Civil Detainee - Conditions of Confinement

FORFEITURE/PENALTY
- ☐ 625 Drug Related Seizure of Property 21 USC 881
- ☐ 690 Other

LABOR
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Management Relations
- ☐ 740 Railway Labor Act
- ☐ 751 Family and Medical Leave Act
- ☐ 790 Other Labor Litigation
- ☐ 791 Employee Retirement Income Security Act

IMMIGRATION
- ☐ 462 Naturalization Application
- ☐ 465 Other Immigration Actions

BANKRUPTCY
- ☐ 422 Appeal 28 USC 158
- ☐ 423 Withdrawal 28 USC 157

INTELLECTUAL PROPERTY RIGHTS
- ☐ 820 Copyrights
- ☒ 830 Patent
- ☐ 835 Patent - Abbreviated New Drug Application
- ☐ 840 Trademark
- ☐ 880 Defend Trade Secrets Act of 2016

SOCIAL SECURITY
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g))
- ☐ 864 SSID Title XVI
- ☐ 865 RSI (405(g))

FEDERAL TAX SUITS
- ☐ 870 Taxes (U.S. Plaintiff or Defendant)
- ☐ 871 IRS—Third Party 26 USC 7609

OTHER STATUTES
- ☐ 375 False Claims Act
- ☐ 376 Qui Tam (31 USC 3729(a))
- ☐ 400 State Reapportionment
- ☐ 410 Antitrust
- ☐ 430 Banks and Banking
- ☐ 450 Commerce
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced and Corrupt Organizations
- ☐ 480 Consumer Credit (15 USC 1681 or 1692)
- ☐ 485 Telephone Consumer Protection Act
- ☐ 490 Cable/Sat TV
- ☐ 850 Securities/Commodities/ Exchange
- ☐ 890 Other Statutory Actions
- ☐ 891 Agricultural Acts
- ☐ 893 Environmental Matters
- ☐ 895 Freedom of Information Act
- ☐ 896 Arbitration
- ☐ 899 Administrative Procedure Act/Review or Appeal of Agency Decision
- ☐ 950 Constitutionality of State Statutes

V. ORIGIN *(Place an "X" in One Box Only)*

☒ 1 Original Proceeding ☐ 2 Removed from State Court ☐ 3 Remanded from Appellate Court ☐ 4 Reinstated or Reopened ☐ 5 Transferred from Another District *(specify)* ☐ 6 Multidistrict Litigation - Transfer ☐ 8 Multidistrict Litigation - Direct File

VI. CAUSE OF ACTION

Cite the U.S. Civil Statute under which you are filing ***(Do not cite jurisdictional statutes unless diversity)***:
35 USC Section 271

Brief description of cause:
patent infringement

VII. REQUESTED IN COMPLAINT:

☐ CHECK IF THIS IS A **CLASS ACTION** UNDER RULE 23, F.R.Cv.P.

DEMAND $

CHECK YES only if demanded in complaint:
JURY DEMAND: ☒ Yes ☐ No

VIII. RELATED CASE(S) IF ANY

(See instructions): JUDGE _____ DOCKET NUMBER _____

DATE
10/26/2021

SIGNATURE OF ATTORNEY OF RECORD
/Woodrow H. Pollack/

FOR OFFICE USE ONLY

RECEIPT # _____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____

INSTRUCTIONS FOR ATTORNEYS COMPLETING CIVIL COVER SHEET FORM JS 44

Authority For Civil Cover Sheet

The JS 44 civil cover sheet and the information contained herein neither replaces nor supplements the filings and service of pleading or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. Consequently, a civil cover sheet is submitted to the Clerk of Court for each civil complaint filed. The attorney filing a case should complete the form as follows:

I.(a) Plaintiffs-Defendants. Enter names (last, first, middle initial) of plaintiff and defendant. If the plaintiff or defendant is a government agency, use only the full name or standard abbreviations. If the plaintiff or defendant is an official within a government agency, identify first the agency and then the official, giving both name and title.

(b) County of Residence. For each civil case filed, except U.S. plaintiff cases, enter the name of the county where the first listed plaintiff resides at the time of filing. In U.S. plaintiff cases, enter the name of the county in which the first listed defendant resides at the time of filing. (NOTE: In land condemnation cases, the county of residence of the "defendant" is the location of the tract of land involved.)

(c) Attorneys. Enter the firm name, address, telephone number, and attorney of record. If there are several attorneys, list them on an attachment, noting in this section "(see attachment)".

II. Jurisdiction. The basis of jurisdiction is set forth under Rule 8(a), F.R.Cv.P., which requires that jurisdictions be shown in pleadings. Place an "X" in one of the boxes. If there is more than one basis of jurisdiction, precedence is given in the order shown below.
United States plaintiff. (1) Jurisdiction based on 28 U.S.C. 1345 and 1348. Suits by agencies and officers of the United States are included here.
United States defendant. (2) When the plaintiff is suing the United States, its officers or agencies, place an "X" in this box.
Federal question. (3) This refers to suits under 28 U.S.C. 1331, where jurisdiction arises under the Constitution of the United States, an amendment to the Constitution, an act of Congress or a treaty of the United States. In cases where the U.S. is a party, the U.S. plaintiff or defendant code takes precedence, and box 1 or 2 should be marked.
Diversity of citizenship. (4) This refers to suits under 28 U.S.C. 1332, where parties are citizens of different states. When Box 4 is checked, the citizenship of the different parties must be checked. (See Section III below; **NOTE: federal question actions take precedence over diversity cases.**)

III. Residence (citizenship) of Principal Parties. This section of the JS 44 is to be completed if diversity of citizenship was indicated above. Mark this section for each principal party.

IV. Nature of Suit. Place an "X" in the appropriate box. If there are multiple nature of suit codes associated with the case, pick the nature of suit code that is most applicable. Click here for: Nature of Suit Code Descriptions.

V. Origin. Place an "X" in one of the seven boxes.
Original Proceedings. (1) Cases which originate in the United States district courts.
Removed from State Court. (2) Proceedings initiated in state courts may be removed to the district courts under Title 28 U.S.C., Section 1441.
Remanded from Appellate Court. (3) Check this box for cases remanded to the district court for further action. Use the date of remand as the filing date.
Reinstated or Reopened. (4) Check this box for cases reinstated or reopened in the district court. Use the reopening date as the filing date.
Transferred from Another District. (5) For cases transferred under Title 28 U.S.C. Section 1404(a). Do not use this for within district transfers or multidistrict litigation transfers.
Multidistrict Litigation – Transfer. (6) Check this box when a multidistrict case is transferred into the district under authority of Title 28 U.S.C. Section 1407.
Multidistrict Litigation – Direct File. (8) Check this box when a multidistrict case is filed in the same district as the Master MDL docket.
PLEASE NOTE THAT THERE IS NOT AN ORIGIN CODE 7. Origin Code 7 was used for historical records and is no longer relevant due to changes in statute.

VI. Cause of Action. Report the civil statute directly related to the cause of action and give a brief description of the cause. **Do not cite jurisdictional statutes unless diversity.** Example: U.S. Civil Statute: 47 USC 553 Brief Description: Unauthorized reception of cable service.

VII. Requested in Complaint. Class Action. Place an "X" in this box if you are filing a class action under Rule 23, F.R.Cv.P.
Demand. In this space enter the actual dollar amount being demanded or indicate other demand, such as a preliminary injunction.
Jury Demand. Check the appropriate box to indicate whether or not a jury is being demanded.

VIII. Related Cases. This section of the JS 44 is used to reference related pending cases, if any. If there are related pending cases, insert the docket numbers and the corresponding judge names for such cases.

Date and Attorney Signature. Date and sign the civil cover sheet.

AO 440 (Rev. 06/12) Summons in a Civil Action

UNITED STATES DISTRICT COURT

for the

Middle District of Florida

AZURITY PHARMACEUTICALS, INC.

Plaintiff(s)

v.

CORERX, INC.

Defendant(s)

Civil Action No. 8:21-cv-2515

SUMMONS IN A CIVIL ACTION

To: *(Defendant's name and address)* CORERX, INC.
14205 MYERLAKE CIRCLE
CLEARWATER, FL 33760

A lawsuit has been filed against you.

Within 21 days after service of this summons on you (not counting the day you received it) — or 60 days if you are the United States or a United States agency, or an officer or employee of the United States described in Fed. R. Civ. P. 12 (a)(2) or (3) — you must serve on the plaintiff an answer to the attached complaint or a motion under Rule 12 of the Federal Rules of Civil Procedure. The answer or motion must be served on the plaintiff or plaintiff's attorney, whose name and address are: Woodrow H. Pollack,
Shutts and Bowen, LLP
4301 W. Boy Scout Blvd #300
Tampa, FL 33607

If you fail to respond, judgment by default will be entered against you for the relief demanded in the complaint. You also must file your answer or motion with the court.

CLERK OF COURT

Date: _____

_____
Signature of Clerk or Deputy Clerk

AO 440 (Rev. 06/12) Summons in a Civil Action (Page 2)

Civil Action No. 8:21-cv-2515

PROOF OF SERVICE

(This section should not be filed with the court unless required by Fed. R. Civ. P. 4 (l))

This summons for *(name of individual and title, if any)* _____

was received by me on *(date)* _____ .

❒ I personally served the summons on the individual at *(place)* _____

_____ on *(date)* _____ ; or

❒ I left the summons at the individual's residence or usual place of abode with *(name)* _____

_____ , a person of suitable age and discretion who resides there,

on *(date)* _____ , and mailed a copy to the individual's last known address; or

❒ I served the summons on *(name of individual)* _____ , who is

designated by law to accept service of process on behalf of *(name of organization)* _____

_____ on *(date)* _____ ; or

❒ I returned the summons unexecuted because _____ ; or

❒ Other *(specify):*

My fees are $ _____ for travel and $ _____ for services, for a total of $ 0 .

I declare under penalty of perjury that this information is true.

Date: _____

_____

Server's signature

_____

Printed name and title

_____

Server's address

Additional information regarding attempted service, etc:

EXHIBIT B

IN THE UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF FLORIDA
TAMPA DIVISION

AZURITY PHARMACEUTICALS, INC.,	)	
Plaintiff,	)	
v.	)	C.A. No. 8:21-cv-2515-TPB-SPF
CORERX, INC.,	)	
Defendant.	)	

NOTICE OF DISMISSAL WITHOUT PREJUDICE

Plaintiff Azurity Pharmaceuticals, Inc. hereby notifies the Court of the dismissal **without prejudice** of all claims against Defendant CoreRx, Inc. pursuant to Federal Rule of Civil Procedure 41(a)(1)(A). Defendant has neither served an answer nor a motion for summary judgment in this action.

Dated: November 26, 2021

Respectfully submitted,

/s/ Woodrow H. Pollack
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4301 W Boy Scout Blvd Ste 300
Tampa, FL 33607-5716
(813) 463-4894

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Los Angeles, CA 90071
(323) 210-2900

CERTIFICATE OF SERVICE

I HEREBY CERTIFY that on November 26, 2021 a true and correct copy of the foregoing was filed electronically and served by mail on anyone unable to accept electronic filing. Notice of this filing will be sent via e-mail to all parties by operation of the Court's electronic filing system or by mail to anyone unable to accept electronic filing as indicated on the Notice of Electronic Filing. Parties may access this filing through the Court's CM/ECF System.

/s/ Woodrow H. Pollack
Woodrow H. Pollack

EXHIBIT C

IN THE UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF FLORIDA

AZURITY PHARMACEUTICALS, INC.,	)	
Plaintiff,	)	
v.	)	C.A. No. 8:21-cv-2515-TPB-SPF
CORERX, INC.,	)	
Defendant.	)	

JOINT MOTION TO REOPEN CASE FOR LIMITED PURPOSE OF CORRECTING DISMISSAL

Plaintiff Azurity Pharmaceuticals, Inc. and Defendant CoreRx, Inc., respectfully ask the Court to reopen the above captioned case for the sole purpose of filing a corrected stipulated dismissal, attached hereto as Exhibit A.

Dated: December 10, 2021

Respectfully submitted,

/s/ Geoffrey Grivner
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Kody M. Sparks (#6464)
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kody.sparks@bipc.com

Attorneys for Defendant, CoreRX, Inc

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IN THE UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF FLORIDA

AZURITY PHARMACEUTICALS, INC.,	)	
Plaintiff,	)	
v.	)	C.A. No. 8:21-cv-2515-TPB-SPF
CORERX, INC.,	)	
Defendant.	)	

JOINT STIPULATION OF DISMISSAL WITHOUT PREJUDICE

Plaintiff Azurity Pharmaceuticals, Inc. and Defendant CoreRx, Inc., hereby agree and stipulate to the dismissal **without prejudice** of all claims against Defendant CoreRx, Inc. pursuant to Federal Rule of Civil Procedure 41(a)(1)(A). Each party shall bear its own costs and attorneys' fees.

Dated: December 10, 2021

Respectfully submitted,

/s/ Geoffrey Grivner
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Kody M. Sparks (#6464)
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kody.sparks@bipc.com

Attorneys for Defendant, CoreRX, Inc.

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EXHIBIT D

UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF FLORIDA
TAMPA DIVISION

AZURITY PHARMACEUTICALS, INC.,	)	
Plaintiff,	)	
v.	)	Case No. 8:21-cv-2515-TPB-SPF
CORERX, INC.,	)	
Defendant,	)	
v.	)	
BIONPHARMA INC.,	)	
Intervenor-Defendant (Motion Pending)	)	

THIRD-PARTY BIONPHARMA INC.'S MOTION TO INTERVENE AND MEMORANDUM OF LAW IN SUPPORT

Third-party Bionpharma Inc. ("Bionpharma") respectfully moves this Court pursuant to Fed. R. Civ. P. 24(a)(2) and 24(b)(1)(B) for leave to intervene as a defendant. Bionpharma does not seek to reopen this case; Bionpharma only seeks to intervene to oppose the Joint Motion to Reopen Case for Limited Purpose of Correcting Dismissal (D.I. 18, "Joint Motion"), which seeks to deprive Bionpharma of a claim preclusion defense it has in parallel, related litigation involving the same accused product and asserted patents that are at issue here.

Broadly speaking, Bionpharma seeks leave to intervene in this action to

defend and exonerate its 1 mg/mL enalapril maleate oral solution prescription drug product ("Bionpharma's ANDA product"), and to dispell the cloud of litigation that threatens its manufacturing and supplier relationships, such as that with Defendant CoreRx, Inc. ("CoreRx").

More particularly, Bionpharma has a compelling interest in opposing the Joint Motion (D.I. 18), as the resolution of that Motion will impact a pending motion to dismiss that Bionpharma has filed in connection with related litigation between Azurity and Bionpharma currently pending in the District of Delaware. Bionpharma is attempting to prevent an end-run around prior decisions adverse to Plaintiff with respect to the patents-in-suit. Granting this motion will not prejudice the rights of any existing party, and it appears that no party wishes for this case to be reopened (*id.*). Denying the motion, however, will greatly prejudice the interests of Bionpharma.

Before the case was dismissed, Plaintiff Azurity Pharmaceuticals, Inc. ("Azurity") indicated that it opposes a motion by Bionpharma to intervene in the case, while CoreRx did not consent but did not state that it would oppose this Motion.

INTRODUCTION AND FACTUAL BACKGROUND

Bionpharma is a generic drug company that develops and commercially markets affordable quality generic medications. In 2018, Bionpharma prepared and filed with the U.S. Food and Drug Administration ("FDA") Abbreviated New Drug

Application ("ANDA") No. 212408 ("Bionpharma's ANDA"), which sought FDA approval to market a 1 mg/ml enalapril maleate oral solution as generic to Azurity's Epaned® antihypertensive prescription drug product ("Bionpharma's ANDA product"). Bionpharma's ANDA was approved on August 10, 2021, and Bionpharma commercially launched its ANDA product shortly thereafter.

In response to the filing of Bionpharma's ANDA, Azurity began instituting what would become three waves of lawsuits against Bionpharma in the United States District Court for the District of Delaware before the Honorable Leonard P. Stark, alleging that Biopharma's ANDA and ANDA product infringe Azurity's Epaned® patent estate ("the Delaware Suits"). The First[1] and Second[2] Wave Suits were resolved in Bionpharma's favor,[3] and the Third Wave Suits,[4] which assert the same patents asserted here against CoreRx,[5] remain pending after Bionpharma recently defeated a preliminary injunction motion from Azurity seeking to remove

[1] *Silvergate Pharm., Inc. v. Bionpharma Inc.*, C.A. Nos. 18-1962-LPS and 19-1067-LPS (D. Del.). Azurity is successor-in-interest to Silvergate Pharmaceuticals, Inc., the named plaintiff in the First and Second Wave Suits.

[2] *Silvergate Pharm., Inc. v. Bionpharma Inc.*, C.A. No. 20-1256-LPS (D. Del.).

[3] *See Silvergate Pharm., Inc. v. Bionpharma Inc.*, C.A. No. 18-1962-LPS, 2021 WL 1751148 (D. Del. Apr. 29, 2021); *Silvergate Pharm., Inc. v. Bionpharma Inc.*, C.A. No. 20-1256-LPS (D. Del.), D.I. 106, Joint Stipulation of Dismissal.

[4] *Azurity Pharm., Inc. v. Bionpharma Inc.*, C.A. Nos. 21-1286-LPS, 21-1455 LPS (D. Del.).

[5] U.S. Patent Nos. 11,040,023 ("'023 patent") and 11,141,405 ("'405 patent") (collectively, "the patents-in-suit").

Bionpharma's ANDA product from the market.[6]

Over three years after Azurity began instituting the Delaware Suits, in what appears to be an attempt to circumvent Judge Stark's rulings, Azurity brings this action against CoreRx, the company that Bionpharma contracted with to (in collaboration with Bionpharma) develop Bionpharma's ANDA product, and to commercially manufacture and supply Bionpharma's ANDA product, alleging that, *inter alia*, CoreRx's commercial manufacture and supply of Bionpharma's ANDA product infringes the patents-in-suit. D.I. 1, Compl. ¶ 1. Azurity also filed an essentially duplicative action against CoreRx in the District of Delaware. *Azurity Pharm., Inc. v. CoreRx, Inc.*, C.A. No. 21-1522-LPS (D. Del.) ("Delaware CoreRx suit"), D.I. 1, Compl.

Bionpharma clearly has an interest in the subject matter of this litigation—the continued, uninterrupted manufacture and supply of its ANDA product. However, Azurity is owned by NovaQuest Capital Management ("NovaQuest"), a private equity firm,[7] and earlier this year NovaQuest acquired CoreRx.[8] Because of the

[6] *See Azurity Pharm., Inc. v. Bionpharma Inc.*, C.A. No. 21-1286-LPS (D. Del.), D.I. 87, Oral Order.

[7] Ex. B, M&A Deal Summary, *NovaQuest Capital Management Acquires Azurity Pharmaceutical*, MERGR.COM, https://mergr.com/novaquest-capital-management-acquires-azurity-pharmaceuticals (last visited Nov. 12, 2021).

[8] Ex. C, *NovaQuest Private Equity Acquires CoreRx, Inc.*, BUSINESS WIRE (Jan. 19, 2021), https://www.businesswire.com/news/home/20210119005200/en/NovaQuest-Private-Equity-Acquires-CoreRx-Inc.

common ownership between Azurity, Bionpharma's competitor, and CoreRx, Bionpharma's commercial manufacturer and supplier,[9] Bionpharma has reason to believe that its interest in the subject of this action may not be adequately represented.[10] Thus, Bionpharma respectfully seeks leave to intervene as a matter of right pursuant to Fed. R. Civ. P. 24(a)(2). Alternatively, the patents-in-suit are also being asserted against Bionpharma in the Third Wave Suits, and Bionpharma has raised non-infringement and invalidity defenses that share with the instant action common questions of law and fact. Thus, permissive intervention under Fed. R. Civ. P. 24(b)(1)(B) is warranted.

Finally, on November 26, 2021, Azurity voluntarily dismissed the instant action and the Delaware CoreRx suit. D.I. 16, Notice of Dismissal; Delaware CoreRx suit, D.I. 6, Notice of Dismissal. By operation of law, the second of those two voluntary dismissals was a adjudication upon the merits and, thus, a with

[9] Upon information and belief, NovaQuest owns and controls Azurity and CoreRx through an intermediate holding company, CutisPharma,. Ex. D, *NovaQuest Capital Management Acquires CutisPharma, Inc.*, PR NEWSWIRE (Mar. 26, 2018), https://www.prnewswire.com/news-releases/novaquest-capital-management-acquires-cutispharma-inc-300619121.html. Azurity identifies CutisPharma Intermediate Holdings Inc. as owning 10% or more of its stock. D.I. 3, Pl.'s L.R. 3.03 Disclosure Statement.

[10] Because the plaintiff patent owner (Azurity) and defendant accused infringer (CoreRx) are actually commonly-owned affiliates, there is no justiciable case or controversy between adverse litigants sufficient to support subject matter jurisdiction over Azurity's patent infringement claims against CoreRx. *MedImmune, Inc. v. Genentech, Inc.*, 549 U.S. 118, 127 (2007). As such, Bionpharma has raised a subject matter jurisdiction defense in its proposed answer (Ex. A) and, if permitted to intervene, will explain to the Court that Azurity's Joint Motion (D.I. 18) should be denied because, *inter alia*, the instant lawsuit and a duplicative suit Azurity filed against CoreRx in Delaware represent sham litigation that was about enforcing legitimate patent rights.

prejudice dismissal of Azurity's infringement claims against CoreRx and, in particular, Bionpharma's ANDA product. FED. R. CIV. P. 41(a)(1)(B). Because Bionpharma and CoreRx are in privity with respect to Bionpharma's ANDA product and Azurity's '023 and '405 patent infringement claims, Bionpharma has moved to dismiss the Third Wave Suits on claim preclusion grounds and the "two dismissal rule" of Rule 41(a)(1)(B).[11] In response, Azurity has filed in the instant action Joint Motion to vacate its own notice of dismissal. D.I. 18. Because the granting of the Joint Motion could potentially deprive Bionpharma of its non-infringement defense based on the "two dismissal rule" and claim preclusion, and undermine Bionpharma's pending Motion to Dismiss the Third Wave Suits, Bionpharma has a compelling interest in opposing the Joint Motion which is not adequately represented by the existing parties in this action.

For the foregoing reasons, explained more fully below, Bionpharma respectfully requests that it be granted leave to intervene as a defendant in this action, and attaches hereto as Exhibit A its proposed Answer in Intervention.[12]

ARGUMENT

I. LEGAL STANDARD

To intervene by right, a movant must show: (1) its application to intervene is

[11] *Azurity Pharm., Inc. v. Bionpharma Inc.*, C.A. No. 21-1286-LPS (D. Del.), D.I. 97; *Azurity Pharm., Inc. v. Bionpharma Inc.*, C.A. No. 21-1455 LPS (D. Del.), D.I. 12.

[12] Exhibit A (Bionpharma's Answer in Intervention) is submitted herewith as required by Fed. R. Civ. P. 24. Bionpharma does not, however, seek to reopen this case.

timely; (2) it has an interest relating to the property or transaction which is the subject of the action; (3) it is so situated that disposition of the action, as a practical matter, may impede or impair its ability to protect that interest; and (4) its interest is represented inadequately by the existing parties to the suit. Fed. R. Civ. P. 24(a)(2); *Tech. Training Assocs., Inc. v. Buccaneers Ltd. P'ship*, 874 F.3d 692, 695-96 (11th Cir. 2017). For permissive intervention, a movant must show: (1) its motion is timely; (2) it has a claim or defense that shares a common question of law or fact with the main action; and (3) its intervention will not cause undue delay or prejudice the rights of the original parties. FED. R. CIV. P. 24(b)(1)(B); *Chiles v. Thornburgh*, 865 F.2d 1197, 1213 (11th Cir. 1989).

II. BIONPHARMA SHOULD BE GRANTED INTERVENTION AS A MATTER OF RIGHT

Fed. R. Civ. P. 24(a)(2) provides the Court, on timely motion, "must permit" "anyone to intervene who … claims an interest relating to the property or transaction that is the subject of the action, and is so situated that disposing of the action may as a practical matter impair or impede the movant's ability to protect its interest, unless existing parties adequately represent that interest." Bionpharma meets all of these requirements and is entitled to intervene as a matter of right.

A. Bionpharma's Motion is Timely

In determining whether a motion to intervene is timely, courts consider: (1) the length of time during which the proposed intervenor knew or reasonably should

have known of its interest in the case before moving to intervene; (2) the extent of prejudice to the existing parties as a result of the proposed intervenor's failure to move for intervention as soon as it knew or should have known about its interest; (3) the extent of prejudice to the proposed intervenor if the motion is denied; and (4) the existence of unusual circumstances militating either for or against a determination that the motion to intervene was timely. *Ga. v. U.S. Army Corp. of Eng'rs*, 302 F.3d 1242, 1259 (11th Cir. 2002) (citation omitted).

Bionpharma files this Motion mere hours after Azurity's and CoreRx's attempt to modify Azurity's own voluntary notice of dismissal (D.I. 18). Bionpharma's motion therefore does not prejudice the other parties. Bionpharma moved for intervention as soon as it knew or should have known about its interest and Azurity's attempt to modify its own notice of dismissal. *See Fla. Med. Ass'n v. Dept. of Health, Educations & Welfare*, No. 3:78-cv-178-J-34MCR, 2011 WL 4459387, at *5-6, *8-9, *16 (M.D. Fla. Sept. 26, 2011).

Regarding the third factor, Bionpharma should be allowed to intervene to defend the manufacture and commercialization of its ANDA product, or it will suffer substantial prejudice. Plaintiff has alleged that Bionpharma's product infringes in other venues, so Bionpharma would suffer great prejudice if it is not allowed to oppose what will amount to a procedural end-run around adverse rulings elsewhere. No unusual circumstances exist for finding Bionpharma's motion is not timely.

Thus, Bionpharma respectfully submits that the Motion is timely.

B. Bionpharma Has an Enormous Interest in the Subject Matter of this Litigation

As to the second element, a non-party has a sufficient interest in the property or transaction at issue when the nonparty has a "direct, substantial, legally protectable interest in the proceedings." *Chiles*, 865 F.2d at 1213.

As explained above, Bionpharma contracted with CoreRx to, in collaboration with Bionpharma, develop Bionpharma's ANDA product, and CoreRx currently commercially manufactures and supplies Bionpharma's ANDA product. Bionpharma has been commercially marketing its ANDA product in the United States since August 17, 2021, and is currently enjoying a 180-day period of non-patent marketing exclusivity granted to Bionpharma by FDA because Bionpharma was the first generic drug company to develop and seek approval for a generic version of Epaned® prior to the expiration of Azurity's Epaned® patents. *See* 21 U.S.C. § 355(j)(5)(B)(iv). Bionpharma also recently defeated a preliminary injunction motion from Azurity seeking to remove Bionpharma's ANDA product from the market based on one of the two patents-in-suit (the '023 patent). *See Azurity Pharm., Inc. v. Bionpharma Inc.*, C.A. No. 21-1286-LPS (D. Del.), D.I. 87, Oral Order.

In its Complaint, Azurity alleges that "CoreRx's manufacture, use, sale, importation, and/or offer to sell and/or inducement of or contributing to others to do

the foregoing within the United States of [Bionpharma's ANDA product] prior to the expiration of the patents-in-suit" constitutes infringement of the patents-in-suit, and seeks, *inter alia*, to enjoin CoreRx from manufacturing and supplying Bionpharma's ANDA product. D.I. 1, Compl. ¶¶ 1, 33-57; *id*. at Prayer for Relief. Thus, Bionpharma has an enormous interest in the subject matter of this litigation, and Azurity recognizes this: in its Local Rule 3.03 Disclosure Statement (D.I. 3), Azurity represents that Bionpharma is an "entity which is likely to be an active participant in the proceedings." D.I. 3, Pl.'s L.R. 3.03 Disclosure Statement at 2. Moreover, Bionpharma and Azurity have been litigating Bionpharma's ANDA product and Azurity's Epaned® patents for the last three years in the District of Delaware, and are currently litigating the alleged infringement of the patents-in-suit by Bionpharma's ANDA product in that court. The nearly complete overlap in the subject matter of the instant suit and the Third Wave Suits—which also involve the patents-in-suit and Bionpharma's ANDA product—is further evidence of the enormous interest Bionpharma has in the subject of this litigation.

Finally, as explained above, because Azurity has voluntarily dismissed the instant action and the duplicative Delaware CoreRx suit, Bionpharma has a claim preclusion defense that is currently the subject of a motion to dismiss that Bionpharma has filed in the Third Wave Suits in Delaware based on the "two dismissal rule" of Fed. R. Civ. P. 41(a)(1)(B). Azurity seeks to deprive Bionpharma

of this defense by jointly moving to re-open this case for the limited purpose of substituting its notice of dismissal with a joint stipulation of dismissal without prejudice. Bionpharma should be allowed the opportunity to explain to this Court why the Joint Motion should be denied, including because Azurity has misused the Federal courts by filing sham litigation against a commonly-owned affiliate, CoreRx.

For at least the foregoing reasons, Bionpharma has a sufficient interest in this litigation justifying intervention as of right.

C. Disposal of this Action Without Bionpharma's Participation Would Prejudice Bionpharma's Ability to Protect Its Interest

Unless Bionpharma is allowed to intervene in this action, its interests would not be adequately protected. *Chiles*, 865 F.2d at 1214. Progression of the case without Bionpharma's involvement would risk inconsistent rulings and judgments with the Third Wave Suits currently pending in the District of Delaware. Bionpharma has been involved in litigation with Azurity over Bionpharma's ANDA product and Azurity's Epaned® patents for the last three years in the District of Delaware, and is currently litigating the patents-in-suit there and whether Bionpharma's ANDA product infringes those patents. *See* the Third Wave Suits; *see also Honeywell Int'l Inc. v. Audiovox Commc'ns Corp.*, C.A. No. 04-1337-KAJ, 2005 WL 2465898 at *1, 4 (D. Del. May 18, 2005) (granting motion to intervene "because it puts a willing manufacturer defendant in the forefront of litigation aimed

squarely at its product."). Disposal of this suit without Bionpharma's involvement may impede Bionpharma's ability to ensure that its ANDA product is found to not infringe any valid claim of the patents-in-suit, and to ensure that Bionpharma is able to continue marketing its ANDA product and providing consumers with a lower-priced generic alternative to Epaned®.

D. Bionpharma's Interest Is Represented Inadequately by the Existing Parties

The fourth factor, that the interest is represented inadequately by the existing parties to the suit, requires a "minimal" showing "that representation of [one's] interest 'may be' inadequate." *Chiles*, 865 F.2d at 1214 (citing *Trbovich v. United Mine Workers of Am.*, 404 U.S. 528, 538 n.10 (1972) (granting intervention as of right)). Bionpharma needs to show only the possibility that its interests may be different than CoreRx. *Id*. at 1214-15. As explained above, NovaQuest, which owns Azurity, recently acquired CoreRx. Thus, because of the common ownership between Azurity, the Plaintiff patent owner in this suit, and CoreRx, the accused infringer, Bionpharma has a reasonable basis to believe that its interest in the subject matter of this litigation may be different, and therefore, inadequately represented by the current parties.[13] Further, Bionpharma is "uniquely situated to understand and defend its own product," *Honeywell*, 2005 WL 2465898, at *4, and therefore meets

[13] Indeed, as Bionpharma will explain if allowed to intervene, there is likely no justiciable case or controversy between adverse litigants sufficient to support this Court's exercise of subject matter jurisdiction over Azurity's patent infringement claims against CoreRx.

the "minimal" standard for showing inadequate representation. Bionpharma thus respectfully submits that it should be granted intervention as a matter of right under Fed. R. Civ. P. 24(a).

III. ALTERNATIVELY, BIONPHARMA SHOULD BE GRANTED PERMISSIVE INTERVATION

Bionpharma's motion is timely and satisfies each of the factors required for intervention as of right. But even if the Court concluded otherwise, it may nevertheless permit intervention on a motion to intervene if it finds that Bionpharma "has a claim or defense that shares with the main action a common question of law or fact." FED. R. CIV. P. 24(b)(1)(B). Here, Bionpharma has claims and defenses that have questions of law and fact in common with this action, such as non-infringement and invalidity in response to Plaintiff's infringement contentions with respect to the patents-in-suit.

A proposed permissive intervenor must show: (1) its motion to intervene is timely; and (2) its defense and the main action share a common question of law or fact. *Chiles*, 865 F.2d at 1213.

A. Bionpharma's Motion is Timely

As explained above in connection with Bionpharma's arguments to support intervention as a matter of right, this Motion is timely.

B. This Action is Duplicative of the Delaware Suits

Bionpharma has claims and defenses to the patents-in-suit that share common

questions of law and fact with this action: namely, the invalidity of the patents-in-suit, and the non-infringement of Bionpharma's ANDA product. In fact, Bionpharma and Azurity are already litigating those claims and defenses in connection with the currently pending Third Wave Suits in Delaware. Bionpharma's invalidity and non-infringement defenses are presumably be the same defenses that CoreRx will be expected to raise here. Thus, it cannot be disputed that Bionpharma has claims and defenses that share common questions of law and fact with this suit.

C. Intervention Will Not Cause Delay or Prejudice the Rights of Azurity or CoreRx

Finally, Bionpharma brings this Motion before CoreRx has even responded to the Complaint. (D.I. 16.) Bionpharma does not seek to reopen this case; only to oppose the Joint Motion (D.I. 18), which seeks to deprive Bionpharma of a claim preclusion defense that Bionpharma has to the patents-in-suit involving the same accused product in the instant suit. However, should this case be reopened and go forward, Bionpharma's defenses will likely overlap completely with CoreRx's defenses. Thus, intervention will impose no delay in resolving this action (and may in fact speed it up given Bionpharma's familiarity with, and history litigating, Azurity's Epaned® patent family).

Furthermore, intervention by Bionpharma would not prejudice the rights of Azurity or CoreRx in any way. Bionpharma and Azurity are already competitors actively litigating the same patents and accused activity in this action in connection

with the Third Wave Suits currently pending in the District of Delaware. Meanwhile, CoreRx and Bionpharma are in privity with one another as to the development and commercialization of Bionpharma's ANDA product, and thus likely have the same defenses to Azurity's infringement claims. As such, Bionpharma respectfully requests that it be granted permission to intervene.

CONCLUSION

Bionpharma respectfully requests that it be allowed to intervene as a matter of right pursuant to Fed. R. Civ. P. 24(a)(2). Alternatively, Bionpharma submits that it meets the requirements for permissive intervention under Fed. R. Civ. P. 24(b)(1)(B), and respectfully requests that it be granted leave to intervene permissively.

LOCAL RULE 3.01(g) CERTIFICATION

Bionpharma hereby certifies that on November 15, 2021, before this case was dismissed, Bionpharma and Azurity conducted a telephonic meet and confer concerning Bionpharma's proposed motion to intervene, and Azurity opposes it.

Bionpharma further certifies that it raised intervention a with CoreRx during a telephone conference held on November 11, 2021. Bionpharma and CoreRx further met and conferred over email, where CoreRx ultimately informed Bionpharma that it would not consent to the Motion; however, CoreRx did not

indicate that it would oppose the Motion.

Dated: December 10, 2021

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of the above document has been furnished, electronically, through the CM/ECF system, to all counsel of record, and via email, noted above, to counsel at TAFT, STETTINIUS & HOLLISTER LLP, and via mail to:

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on this December 10, 2021.

/s/Eleanor M. Yost
Eleanor M. Yost

EXHIBIT A

UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF FLORIDA
TAMPA DIVISION

AZURITY PHARMACEUTICALS, INC.,	)	
Plaintiff,	)	
v.	)	Case No. 8:21-cv-2515-TPB-SPF
CORERX, INC.,	)	
Defendant,	)	
v.	)	
BIONPHARMA INC.,	)	
Intervenor-Defendant	)	

[PROPOSED] INTERVENOR-DEFENDANT BIONPHARMA INC.'S ANSWER, DEFENSES, AND COUNTERCLAIMS IN INTERVENTION

Intervenor-Defendant Bionpharma Inc. ("Bionpharma") by its undersigned counsel, for its Answer, Defenses, and Counterclaims to the Complaint for Patent Infringement (D.I. 1, "Complaint") filed by Plaintiff Azurity Pharmaceuticals, Inc. ("Azurity" or "Plaintiff"), states as follows:

ANSWER

GENERAL DENIAL

Pursuant to Fed. R. Civ. P. 8(b)(3), Bionpharma denies all allegations in Plaintiff's Complaint except those specifically admitted below:

THE NATURE OF THE ACTION

1. This is an action for patent infringement of United States Patent Nos. 11,040,023 (the "'023 patent") and 11,141,405 the "'405 patent") (collectively the "Patents-in-Suit") and damages under the patent laws of the United States, Title 35, United States Code, that arises out of CoreRx's manufacture, use, sale, importation, and/or offer to sell and/or inducement of or contributing to others to do the foregoing within the United States of the product that is the subject of Bionpharma Inc.'s ("Bionpharma") ANDA No. 212408 ("CoreRx Formulation") prior to the expiration of the Patents-in-Suit. Azurity seeks all available relief under the patent laws of the United States, 35 U.S.C. § 100 *et. seq.*, and any other applicable laws for CoreRx's infringement of the Patents-in-Suit.

ANSWER: Paragraph 1 contains legal conclusions and allegations to which no answer is required. To the extent an answer may be required, Bionpharma admits that Azurity's Complaint purports to state an action for infringement of U.S. Patent Nos. 11,040,023 (the "'023 patent") and 11,141,405 the "'405 patent") under Title 35 of the United States Code based on certain activities by Defendant CoreRx, Inc. ("CoreRx") with respect to the product that is the subject of Bionpharma's Abbreviated New Drug Application ("ANDA") No. 212408 ("Bionpharma's ANDA") concerning a 1 mg/mL enalapril maleate oral solution described therein ("Bionpharma's ANDA product"). Bionpharma denies all remaining allegations of paragraph 1.

THE PARTIES

2. Azurity is a corporation organized and existing under the laws of the State of Delaware, with a principal place of business at 8 Cabot Road, Suite 2000, Woburn MA 01801.

ANSWER: Bionpharma lacks knowledge or information sufficient to form a belief about the truth of the allegations contained in paragraph 2, and on that basis denies these allegations.

3. On information and belief, CoreRx is a corporation organized and existing under the laws of the State of Florida, with its principal place of business at 14205 Myerlake Cir., Clearwater, FL 33760. On information and belief, CoreRx is in the business of, among other things, developing, manufacturing, and selling generic copies of branded pharmaceutical products for the U.S. market.

ANSWER: Bionpharma lacks knowledge or information sufficient to form a belief about the truth of the allegations contained in paragraph 3, and on that basis denies these allegations.

JURISDICTION AND VENUE

4. This action arises under the patent laws of the United States of America, 35 U.S.C. § 1, et seq., and from CoreRx's manufacture, use, sale, importation, and/or offer to sell and/or inducement of or contributing to others to do the foregoing within the United States of the CoreRx Formulation before the expiration of the Patents-in-Suit.

ANSWER: Paragraph 4 contains legal conclusions and allegations to which no answer is required. To the extent an answer may be required, denied.

5. This Court has subject matter jurisdiction over the action under 28 U.S.C. §§ 1331, 1338(a) (patent infringement). Relief is sought under 35 U.S.C. §§ 271(a)-(c).

ANSWER: Paragraph 5 contains legal conclusions and allegations to which no answer is required. To the extent an answer may be required, denied.

6. This Court has personal jurisdiction over CoreRx because, among other things, on information and belief, CoreRx is a corporation formed under the laws of the State of Florida that maintains a principal place of business in Florida.

ANSWER: Paragraph 6 contains legal conclusions and allegations to which no answer is required. To the extent an answer may be required, Bionpharma is without sufficient information with which to admit or deny the allegations of Paragraph 6, and therefore denies the allegations of this Paragraph.

7. Venue is proper in this Court under 28 U.S.C. §§ 1391(c) and 1400(b).

ANSWER: Paragraph 7 contains legal conclusions and allegations to which no answer is required. To the extent an answer may be required, denied.

AZURITY'S EPANED® PRODUCT

8. Azurity holds approved NDA No. 208686 for a ready-to-use oral solution of enalapril maleate, which is prescribed and sold under the trade name Epaned®.

ANSWER: Bionpharma lacks knowledge or information sufficient to form a belief about the truth of the allegations contained in paragraph 8, and on that basis denies these allegations.

9. Azurity's Epaned® product is the first FDA approved and labeled ace inhibitor treatment that is a ready-to-use oral solution for hypertension in children under six years of age. Epaned® is also indicated to treat hypertension in adults, heart failure, and asymptomatic left ventricular dysfunction.

ANSWER: Denied.

PATENTS-IN-SUIT

10. The ’023 patent, entitled “Enalapril Formulations,” issued on June 22, 2021. A true and correct copy of the ’023 patent is attached to this Complaint as Exhibit A.

ANSWER: Paragraph 10 contains legal conclusions and allegations to which no answer is required. To the extent an answer may be required, Bionpharma admits that what purports to be a copy of the ’023 patent is attached to the Complaint as Exhibit A; that the ’023 patent is entitled “Enalapril Formulations” and bears an issue date of June 22, 2021. Bionpharma denies any suggestion that the ’023 patent is valid or enforceable. Bionpharma lacks knowledge or information sufficient to form a belief about the truth of the remaining allegations contained in paragraph 10, and on that basis denies these allegations.

11. The ’023 patent was duly and legally issued to Azurity as the assignee and Azurity owns all rights, title, and interest in the ’023 patent.

ANSWER: Paragraph 11 contains legal conclusions and allegations to which no answer is required. To the extent an answer may be required, denied.

12. Pursuant to 21 U.S.C. § 355, the ’023 patent is listed in the Approved Drug Products with Therapeutic Equivalence Evaluations (“the Orange Book”) in connection with Azurity’s Epaned® product.

ANSWER: Paragraph 12 contains legal conclusions and allegations to which no answer is required. To the extent an answer may be required, admitted.

13. The ’023 patent describes stable, oral liquid formulations of enalapril.

ANSWER: Paragraph 13 contains legal conclusions and allegations to which no answer is required. To the extent an answer may be required, denied.

14. The ’023 patent expires on March 25, 2036.

ANSWER: Paragraph 14 contains legal conclusions and allegations to which no answer is required. To the extent an answer may be required, denied.

15. The ’405 patent, entitled “Enalapril Formulations,” issued on October 12, 2021. A true and correct copy of the ’405 patent is attached to this Complaint as Exhibit B.

ANSWER: Paragraph 15 contains legal conclusions and allegations to which no answer is required. To the extent an answer may be required, Bionpharma admits that what purports to be a copy of the ’405 patent is attached to the Complaint as Exhibit B; that the ’405 patent is entitled “Enalapril Formulations” and bears an issue date of October 12, 2021. Bionpharma denies any suggestion that the ’405 patent is valid or enforceable. Bionpharma lacks knowledge or information sufficient to form a belief about the truth of the remaining allegations contained in paragraph 15, and on that basis denies these allegations.

16. The ’405 patent was duly and legally issued to Azurity as the assignee and Azurity owns all rights, title, and interest in the ’405 patent.

ANSWER: Paragraph 16 contains legal conclusions and allegations to which no answer is required. To the extent an answer may be required, denied.

17. Pursuant to 21 U.S.C. § 355, the ’405 patent is listed in the Orange Book in connection with Azurity’s Epaned® product.

ANSWER: Paragraph 17 contains legal conclusions and allegations to which no answer is required. To the extent an answer may be required, admitted.

18. The '405 patent describes stable, oral liquid formulations of enalapril.

ANSWER: Paragraph 18 contains legal conclusions and allegations to which no answer is required. To the extent an answer may be required, denied.

19. The '405 patent expires on March 25, 2036.

ANSWER: Paragraph 19 contains legal conclusions and allegations to which no answer is required. To the extent an answer may be required, denied.

[ALLEGED] INFRINGEMENT BY CORERX

20. On information and belief, CoreRx developed, manufactures, and sells the CoreRx Formulation.

ANSWER: Paragraph 20 contains legal conclusions and allegations to which no answer is required. To the extent an answer may be required, Bionpharma admits that CoreRx, in collaboration with Bionpharma, developed Bionpharma's ANDA product, and that CoreRx manufactures and supplies Bionpharma's ANDA product. Bionpharma denies all remaining allegations of Paragraph 20.

21. On June 22, 2021, Azurity brought an action against Bionpharma alleging that the filing of ANDA No. 212408 was an act of infringement of the '023 patent because the CoreRx Formulation is covered by one or more claims in the '023 patent. That case is captioned *Azurity Pharmaceuticals, Inc. v. Bionpharma Inc.*, C.A. No. 21-1286-LPS (D. Del.) ("the '023 Bionpharma Action").

ANSWER: Paragraph 21 contains legal conclusions and allegations to which no answer is required. To the extent an answer may be required, Bionpharma admits

that Azurity instituted *Azurity Pharmaceuticals, Inc. v. Bionpharma Inc.*, C.A. No. 21-1286-LPS (D. Del.) ("the '023 Bionpharma Action") against Bionpharma. Bionpharma denies all remaining allegations of Paragraph 21.

22. During prior litigation regarding ANDA No. 212408, CoreRx was represented by the same counsel that represented Bionpharma. *See Silvergate Pharmaceuticals, Inc. v. Bionpharma Inc.*, C.A. No. 18-1962-LPS, D.I. 56 (D. Del. Mar. 13, 2020) & C.A. No. 19-1067-LPS, D.I. 68 (D. Del. Mar. 13, 2020).

ANSWER: Paragraph 22 contains legal conclusions and allegations to which no answer is required. To the extent an answer is required, admitted.

23. On information and belief, CoreRx is aware of the '023 Bionpharma Action.

ANSWER: Bionpharma is without sufficient information with which to form a belief as to the allegations of Paragraph 23, and therefore denies those allegations.

24. On information and belief, CoreRx is aware that Azurity, in the '023 Bionpharma Action, filed a motion for preliminary injunction ("Azurity's PI Motion") seeking to enjoin the sale of the CoreRx Formulation.

ANSWER: Bionpharma is without sufficient information with which to form a belief as to the allegations of Paragraph 24, and therefore denies those allegations.

25. On information and belief, CoreRx is aware that Bionpharma, in response to Azurity's PI Motion, does not deny that the CoreRx Formulation infringes several claims of the '023 patent.

ANSWER: Denied.

26. On October 15, 2021, Azurity brought an action against Bionpharma for infringement of the '405 patent. That case is captioned *Azurity*

Pharmaceuticals, Inc. v. Bionpharma Inc., C.A. No. 21-1455-LPS (D. Del.) ("the '405 Bionpharma Action").

ANSWER: Paragraph 26 contains legal conclusions and allegations to which no answer is required. To the extent an answer may be required, Bionpharma admits that Azurity instituted *Azurity Pharmaceuticals, Inc. v. Bionpharma Inc.*, C.A. No. 21-1455-LPS (D. Del.) ("the '405 Bionpharma Action") against Bionpharma. Bionpharma denies all remaining allegations of Paragraph 26.

27. On information and belief, CoreRx is aware of the '405 Bionpharma Action.

ANSWER: Bionpharma is without sufficient information with which to form a belief as to the allegations of Paragraph 27, and therefore denies those allegations.

28. The Patents-in-Suit expire on March 25, 2036.

ANSWER: Paragraph 28 contains legal conclusions and allegations to which no answer is required. To the extent an answer is required, denied.

29. On information and belief, on August 10, 2021, several weeks after the '023 patent legally issued from the United States Patent and Trademark Office and Azurity brought suit for infringement of the '023 patent against Bionpharma, ANDA No. 212408 was approved by FDA. Thereafter, in blatant disregard for Azurity's patent rights, Bionpharma began offering for sale and selling the CoreRx Formulation which, on information and belief, was manufactured by CoreRx.

ANSWER: Paragraph 29 contains legal conclusions and allegations to which no answer is required. To the extent an answer may be required, Bionpharma admits its ANDA was approved by FDA and that it began selling its ANDA product, which

is supplied by CoreRx. Bionpharma denies all remaining allegations of Paragraph 29.

30. On information and belief, CoreRx has and continues to engage in the commercial manufacture and sale of the CoreRx Formulation before the expiration of the Patents-in-Suit with the knowledge and intent to infringe the Patents-in-Suit.

ANSWER: Denied.

31. On information and belief, the CoreRx Formulation infringes at least one claim of the Patents-in-Suit, including at least claim 1 of the '023 patent and claim 1 of the '405 patent, under at least one of 35 U.S.C. § 271(a), (b), and/or (c).

ANSWER: Denied.

32. On information and belief, under 35 U.S.C. § 271(a)-(c), CoreRx has knowingly, willfully, repeatedly, and continually infringed at least one claim of the Patents-in-Suit, including at least claim 1 of the '023 patent and claim 1 of the '405 patent, by manufacturing, using, offering for sale, selling, and/or importing the CoreRx Formulation, and/or inducement of or contributing to others to do the foregoing in the United States before the expiration date of the Patents-in-Suit.

ANSWER: Denied.

CLAIMS FOR RELIEF

Count I—[Alleged] Infringement of the '023 Patent under 35 U.S.C. § 271(a)-(c)

33. Azurity realleges and incorporates paragraphs 1 through 32 as if fully set forth herein.

ANSWER: Bionpharma incorporates its answers to paragraphs 1 through 32 as if fully set forth herein.

34. On information and belief, the CoreRx Formulation has received final approval from FDA.

ANSWER: Paragraph 34 contains legal conclusions and allegations to which no answer is required. To the extent an answer may be required, Bionpharma admits that its ANDA has been approved by FDA. Bionpharma denies all remaining allegations of Paragraph 34.

35. On information and belief, CoreRx has engaged in and/or induced and continues to induce another, including Bionpharma, to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of the CoreRx Formulation. CoreRx's acts of infringement have irreparably injured and damaged and continue to irreparably injure and damage Azurity.

ANSWER: Denied.

36. The commercial manufacture, use, offer for sale, sale, and/or importation of the CoreRx Formulation is an act of direct infringement of one or more claims of the '023 patent under 35 U.S.C. § 271(a), including at least claim 1 of the '023 patent.

ANSWER: Denied.

37. On information and belief, CoreRx is inducing infringement of one or more claims of the '023 patent under 35 U.S.C. § 271(b) by inducing the making, using, offering to sell, selling, and/or importation of the CoreRx Formulation in the United States. On information and belief, CoreRx is intentionally encouraging acts of direct infringement with knowledge of the '023 patent and knowledge that its acts are encouraging infringement.

ANSWER: Denied.

38. On information and belief, CoreRx is contributorily infringing one or more claims of the '023 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing the CoreRx Formulation in the United States. On information and belief, CoreRx,

through offering to sell or selling the CoreRx Formulation, has offered to sell or sold, and continues to do so, within the United States or import into the United States a component of a composition or material for use in practicing one or more claims of the ’023 patent. On information and belief, CoreRx conducts and has conducted such activities knowing such component of a composition or material to be especially adapted for a use that infringes one or more claims of the ’023 patent and is not a staple article or commodity of commerce suitable for substantial noninfringing use.

ANSWER: Denied.

39. The foregoing actions by CoreRx constitute infringement of the ’023 patent.

ANSWER: Denied.

40. CoreRx is committing those acts of infringement without license or authorization.

ANSWER: Denied.

41. CoreRx is committing those acts of infringement despite its knowledge of both the ’023 patent and the ’023 Bionpharma Action.

ANSWER: Denied.

42. Azurity is entitled to a judgement that the commercial manufacture, use, offer for sale, sale, and/or importation of the CoreRx Formulation infringes the ’023 patent.

ANSWER: Denied.

43. Azurity has suffered and will continue to suffer financial harm as a result of CoreRx’s infringing activities.

ANSWER: Denied.

44. The commercial manufacture, use, offer for sale, sale, and/or importation of the CoreRx Formulation in violation of Azurity’s patent

rights has caused and is continuing to cause substantial and irreparable harm to Azurity for which damages are inadequate.

ANSWER: Denied.

45. Azurity is entitled to monetary damages but, because the infringement by CoreRx of the '023 patent will continue to cause Azurity irreparable injury and damage for which there is no adequate remedy at law unless and until CoreRx is enjoined from infringing the '023 patent, Azurity has no complete, adequate remedy at law and, therefore, is entitled to injunctive relief.

ANSWER: Denied.

Count II—[Alleged] Infringement of the '405 Patent under 35 U.S.C. § 271(a)-(c))

46. Azurity realleges and incorporates paragraphs 1 through 32 as if fully set forth herein.

ANSWER: Bionpharma incorporates its answers to paragraphs 1 through 32 as if fully set forth herein.

47. On information and belief, the CoreRx Formulation has received final approval from FDA.

ANSWER: Paragraph 47 contains legal conclusions and allegations to which no answer is required. To the extent an answer may be required, Bionpharma admits that its ANDA has been approved by FDA. Bionpharma denies all remaining allegations of Paragraph 47.

48. On information and belief, CoreRx has engaged in and/or induced and continues to induce another, including Bionpharma, to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of the CoreRx Formulation. CoreRx's acts of infringement have irreparably injured and damaged and continue to irreparably injure and damage Azurity.

ANSWER: Denied.

49. The commercial manufacture, use, offer for sale, sale, and/or importation of the CoreRx Formulation is an act of direct infringement of one or more claims of the ’405 patent under 35 U.S.C. § 271(a), including at least claim 1 of the ’405 patent.

ANSWER: Denied.

50. On information and belief, CoreRx is inducing infringement of one or more claims of the ’405 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing the CoreRx Formulation in the United States. On information and belief, CoreRx is intentionally encouraging acts of direct infringement with knowledge of the ’405 patent and knowledge that its acts are encouraging infringement.

ANSWER: Denied.

51. On information and belief, CoreRx is contributorily infringing one or more claims of the ’405 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing the CoreRx Formulation in the United States. On information and belief, CoreRx, through offering to sell or selling the CoreRx Formulation, has offered to sell or sold, and continues to do so, within the United States or import into the United States a component of a composition or material for use in practicing one or more claims of the ’405 patent. On information and belief, CoreRx conducts and has conducted such activities knowing such component of a composition or material to be especially adapted for a use that infringes one or more claims of the ’405 patent and is not a staple article or commodity of commerce suitable for substantial noninfringing use.

ANSWER: Denied.

52. The foregoing actions by CoreRx constitute infringement of the ’405 patent.

ANSWER: Denied.

53. CoreRx is committing those acts of infringement without license or authorization.

ANSWER: Denied.

54. CoreRx is committing those acts of infringement despite its knowledge of both the ’405 patent and the ’405 Bionpharma Action Azurity is entitled to a judgement that the commercial manufacture, use, offer for sale, sale, and/or importation of the CoreRx Formulation infringes the ’405 patent.

ANSWER: Denied.

55. Azurity has suffered and will continue to suffer financial harm as a result of CoreRx’s infringing activities.

ANSWER: Denied.

56. The commercial manufacture, use, offer for sale, sale, and/or importation of the CoreRx Formulation in violation of Azurity’s patent rights has caused and is continuing to cause substantial and irreparable harm to Azurity for which damages are inadequate.

ANSWER: Denied.

57. Azurity is entitled to monetary damages but, because the infringement by CoreRx of the ’405 patent will continue to cause Azurity irreparable injury and damage for which there is no adequate remedy at law unless and until CoreRx is enjoined from infringing the ’405 patent, Azurity has no complete, adequate remedy at law and, therefore, is entitled to injunctive relief.

ANSWER: Denied.

PRAYER FOR RELIEF

Azurity respectfully requests the following relief:

a) A finding that the Patents-in-Suit are valid and enforceable;

b) A judgment that CoreRx's making, using, offering to sell, or selling in the United States, or importing into the United States of the CoreRx Formulation directly infringes one or more claims of the Patents-in-Suit;

c) A judgment that CoreRx has induced infringement of the Patents-in-Suit by encouraging others to use, sell, offer for sale, and/or import the CoreRx Formulation in the United States before the expiration of the Patents-in-Suit;

d) A judgment that CoreRx has contributorily infringed the Patents-in-Suit by offering to sell or selling the CoreRx Formulation in the United States before the expiration of the Patents-in-Suit, knowing the same is especially adapted for a use that directly infringes the Patents-in-Suit and that there is no substantial non-infringing use for the CoreRx Formulation;

e) A judgment that CoreRx's infringement was and is willful;

f) A finding that Azurity be awarded all damages adequate to compensate it for CoreRx's past infringement and any continuing or future infringement of the Patents-in-Suit in addition to interest and costs;

g) A permanent injunction enjoining CoreRx, and its subsidiaries, parents, officers, agents, servants, employees, licensees, representatives, and attorneys, and all other persons acting or attempting to act in active concert or participation with it or acting on its behalf, from engaging in the commercial manufacture use, offer to sell, or importation into the United States, of any drug product covered by the Patents-in-Suit, including the CoreRx Formulation, until the expiration of the Patents-in-Suit;

h) A finding that CoreRx's infringement is willful and that the monetary damages awarded to Azurity be trebled and include pre- and post-judgment interest, costs, and disbursements pursuant to 35 U.S.C. § 284;

i) A finding that this action for infringement is an exceptional case under 35 U.S.C. § 285, and that CoreRx is responsible for payment of Azurity's attorneys' fees and costs;

j) An award of any such other and further relief as the Court may deem just and proper.

ANSWER: Bionpharma denies Azurity is entitled to any of the relief requested in their Prayer for Relief or otherwise.

BIONPHARMA'S ADDITIONAL DEFENSES

Bionpharma asserts the following defenses without prejudice to the denials in this Answer and without admitting any allegations of the Complaint not otherwise admitted.

FIRST DEFENSE
(INVALIDITY OF THE '023 PATENT)

The claims of the '023 patent are invalid and/or unenforceable under 35 U.S.C. §§ 101, *et seq*. including, *inter alia*, §§ 101, 102, 103, and/or 112, or under other judicially-created bases for invalidation for at least the reasons set forth in Bionpharma's counterclaim Count I.

SECOND DEFENSE
(NO INFRINGEMENT OF THE '023 PATENT)

The manufacture, use, offer for sale, sale, or importation of Bionpharma's ANDA product does not and will not infringe, either literally or under the doctrine of equivalents, either directly or indirectly, any valid and enforceable claim of the '023 patent for at least the reasons set forth in Bionpharma's counterclaim Count II.

THRID DEFENSE
(INVALIDITY OF THE '405 PATENT)

The claims of the '405 patent are invalid and/or unenforceable under 35 U.S.C. §§ 101, *et seq*. including, *inter alia*, §§ 101, 102, 103, and/or 112, or under other judicially-created bases for invalidation for at least the reasons set forth in Bionpharma's counterclaim Count III.

FOURTH DEFENSE
(NO INFRINGEMENT OF THE '405 PATENT)

The manufacture, use, offer for sale, sale, or importation of Bionpharma's ANDA product does not and will not infringe, either literally or under the doctrine of equivalents, either directly or indirectly, any valid and enforceable claim of the '482 patent for at least the reasons set forth in Bionpharma's counterclaim Count IV.

FIFTH DEFENSE
(FAILURE TO STATE A CLAIM)

Azurity's Complaint, in whole and/or in part, fails to state a claim upon which relief can be granted.

SIXTH AFFIRMATIVE DEFENSE
(*RES JUDICATA*; COLLATERAL ESTOPPEL)

Azurity's Complaint is barred on *res judicata* grounds, including on claim preclusion grounds as Azurity's Complaint asserts the same cause of action that was previously litigated and resolved in Bionpharma's favor in *Silvergate Pharmaceuticals, Inc. v. Bionpharma Inc.*, C.A. Nos. 18-1962-LPS, 19-1067-LPS, and 20-1256-LPS (D. Del.), including on claim preclusion grounds because Azurity has voluntarily twice dismissed the same causes of action against CoreRx, and including on collateral estoppel grounds.

SEVENTH AFFIRMATIVE DEFENSE
(DISCLOSURE-DEDICATION)

Plaintiff is legally barred from asserting infringement of certain claims of the

'023 and '405 patents under the disclosure-dedication doctrine.

EIGHTH DEFENSE
(LACK OF SUBJECT MATTER JURISDICTION)

This Court lacks subject matter jurisdiction over the claims in Azurity's Complaint, as those claims fail to state a case or controversy between Azurity and CoreRx.

***

WHEREFORE, Bionpharma requests the Court enter judgment in its favor, award Bionpharma its attorneys' fees, costs of this action, and such other and further relief as the Court deems proper.

BIONPHARMA'S COUNTERCLAIMS

Pursuant to Fed. R. Civ. P. 13 and 24, Intervenor-Defendant Bionpharma Inc. ("Bionpharma") hereby states for its Counterclaims against Plaintiff Azurity Pharmaceuticals, Inc. ("Azurity"), the following:

PARTIES

1. Bionpharma is a corporation organized and existing under the laws of the State of Delaware, with its principal place of business at 600 Alexander Rd., #2-4B, Princeton, NJ 08540. Bionpharma is in the business of, among other things, selling pharmaceutical drug products, including pharmaceutical drug products that Bionpharma has contracted with third parties to develop and supply, such as Defendant CoreRx, Inc. ("CoreRx"), a contract development and manufacturing organization ("CDMO").

2. Upon information and belief, Azurity is a corporation organized and existing under the laws of the State of Delaware, with a principal place of business at 8 Cabot Road, Suite 2000, Woburn, MA 01801. Upon information and belief, Azurity is the successor-in-interest to Silvergate Pharmaceuticals, Inc.

NATURE OF THE ACTION

3. Bionpharma brings this action for a declaratory judgment that U.S. Patent Nos. 11,040,023 ("'023 patent") and 11,141,405 ("'405 patent") (together,

"the patents-in-suit"), which Azurity asserts in the instant suit against CoreRx, are invalid and not infringed.

JURISDICTION, VENUE, AND CONDITIONS PRECEDENT

4. These claims arise under the Patent Laws of the United States, 35 U.S.C. § 1 *et seq.*, and the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

5. This Court has original jurisdiction over the subject matter of these claims under 28 U.S.C. §§ 1331 and 1338(a); and under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

6. This Court has subject matter jurisdiction over these claims for declaratory judgment pursuant to 28 U.S.C. §§ 1331, 1337(a), 1338(a), 2201(a) and (b), and 2202, based on an actual controversy between Bionpharma and Azurity arising under the Patent Laws of the United States, 35 U.S.C. § 1, et seq.

7. This Court has personal jurisdiction over Azurity based on, *inter alia*, the filing of this lawsuit in this jurisdiction.

8. Venue is proper in this judicial district under 28 U.S.C. §§ 1391(b) and (c), and 1400(b).

9. All conditions precedent to this lawsuit have occurred, been satisfied, or been waived.

10. Bionpharma has retained the below listed counsel to represent it in the case, and agreed to pay counsel a reasonable fee for their services.

FACTS COMMON TO ALL COUNTS

11. On or about June 22, 2021, the United States Patent and Trademark Office issued the ’023 patent.

12. Upon information and belief, Azurity is the assignee of the ’023 patent.

13. On or about October 12, 2021, the United States Patent and Trademark Office issued the ’405 patent.

14. Upon information and belief, Azurity is the assignee of the ’405 patent.

15. Azurity purports and claims to have the right to enforce the ’023 and ’405 patents.

16. In 2016, Bionpharma contracted with CoreRx to, in collaboration with Bionpharma, develop a 1 mg/mL enalapril maleate oral solution as generic to Azurity’s Epaned® (enalapril maleate) oral solution, 1 mg/mL, and to commercially manufacture that product for Bionpharma.

17. In 2018, Bionpharma prepared and filed with the U.S. Food and Drug Administration (“FDA”) Abbreviated New Drug Application (“ANDA”) No. 212408, which sought FDA approval for the 1 mg/mL enalapril oral solution product that CoreRx had collaboratively developed with Bionpharma (“Bionpharma’s ANDA”).

18. Bionpharma's ANDA was approved by FDA on or about August 10, 2021, and Bionpharma commercially and lawfully launched its ANDA product on or about August 17, 2021.

19. Pursuant to a Master Manufacturing Supply Agreement effective November 2020 ("MMSA"), CoreRx commercially manufactures and supplies Bionpharma's ANDA product.

20. On information and belief, on or about March 26, 2018, NovaQuest Capital Management ("NovaQuest"), an investment or venture capital firm, acquired a controlling interest in Azurity.

21. On information and belief, on or about January 19, 2021, NovaQuest acquired a controlling interest in CoreRx.

22. On information and belief, NovaQuest controls and/or dominates Azurity through an intermediate holding company, CutisPharma Intermediate Holdings Inc.

23. On information and belief, NovaQuest controls and/or dominates CoreRx through an intermediate holding company, CutisPharma Intermediate Holdings Inc.

24. On or about October 27, 2021, Azurity instituted this action against CoreRx, alleging, *inter alia*, that "CoreRx's manufacture, use, sale, importation, and/or offer to sell and/or inducement of or contributing to others to do the foregoing

within the United States of the product that is the subject of [Bionpharma's] ANDA . . . prior to the expiration of the [p]atents-in-[s]uit" infringes the patents-in-suit. D.I. 1, Compl. ¶ 1.

25. Bionpharma has an interest in the subject matter of the instant action; namely, CoreRx's manufacture and supply of Bionpharma's ANDA product.

26. Disposal of the instant action without Bionpharma's participation would impair or impede Bionpharma's ability to protect its interest in the subject matter of this action.

27. Because of the common ownership between Azurity and CoreRx, Bionpharma has a reasonable belief that CoreRx may not adequately represent Bionpharma's interest in the subject matter of this action.

28. On or about November 11, 2021, Azurity filed a First Amended and Supplemental Complaint for Patent Infringement in the United States District Court for the District of Delaware in *Azurity Pharmaceuticals, Inc. v. Bionpharma, Inc.*, C.A. No. 21-1286-LPS (D. Del.) (D.I. 89) alleging, *inter alia,* that Bionpharma's commercial marketing of its ANDA product directly and indirectly infringes the '023 patent.

29. On or about October 15, 2021, Azurity filed a Complaint for Patent Infringement in the United States District Court for the District of Delaware in *Azurity Pharmaceuticals, Inc. v. Bionpharma, Inc.*, C.A. No. 21-1455-LPS (D. Del.)

alleging, *inter alia*, that Bionpharma's commercial marketing of its ANDA product directly and indirectly infringes the '405 patent.

COUNT I
(Declaratory Judgment of Invalidity of the '023 Patent)

30. Bionpharma realleges and incorporates by reference the allegations of paragraphs 1-29 as though fully set forth herein.

31. There is an actual, substantial, and continuing case or controversy between Bionpharma and the Azurity regarding, *inter alia*, the invalidity of the '023 patent.

32. The claims of the '023 patent are invalid for failure to satisfy one or more of the conditions for patentability in Title 35 of the United States Code, including but not limited, to 35 U.S.C. §§ 101, 102, 103, and/or 112.

33. Claim 1 of the '023 patent, the sole independent claim, recites as follows:

> 1. A stable oral liquid formulation, consisting essentially of:
>
> (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
>
> (ii) a sweetener;
>
> (iii) a preservative, wherein the preservative comprises sodium benzoate, a paraben or a mixture of parabens;
>
> (iv) water; and
>
> (v) optionally a flavoring agent;

wherein the formulation is stable at about 5±3° C. for at least 12 months; and wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

34. The specification of the '023 patent does not contain a written description of the subject matter claimed in the '023 patent, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains to make and use the same. Specifically, nowhere in the specification of the '023 patent is there any description of an enalapril liquid without a buffer, including an enalapril liquid without a buffer that would meet the stability limitations recited in the claims. Moreover, Azurity argued during the prosecution history of the '023 patent, and in connection with *Silvergate Pharmaceuticals, Inc. v. Bionpharma, Inc.*, Nos. 18-1062-LPS, 19-1067-LPS, and 20-1256-LPS (D. Del.), that the stability of enalapril oral liquid formulations was unpredictable and that only through preparation and testing of formulations could a person of ordinary skill ascertain what combination of ingredients would lead to stable formulations. There is nothing in the specification of the '023 patent demonstrating to a person of ordinary skill in the art that the named inventors were in possession of the claimed enalapril oral liquid formulations as of the filing date of the application that issued into the '023 patent, and the claims of the '023 patent are therefore invalid for lack of written description.

35. The claims of the ’023 patent are also invalid for lack of enablement, as the ’023 patent specification does not describe the manner and process of making and using the invention so as to enable a person of skill in the art to make and use the full scope of the invention without undue experimentation. Specifically, nowhere in the specification of the ’023 patent is there any data provided or rationale advanced demonstrating that the claimed enalapril oral liquid formulations, some of which do not include buffers, would be stable at refrigerated conditions for the storage periods recited in the claims. Moreover, Azurity argued during the prosecution history of the ’023 patent, and in connection with *Silvergate Pharmaceuticals, Inc. v. Bionpharma, Inc.*, Nos. 18-1062-LPS, 19-1067-LPS, and 20-1256-LPS (D. Del.), that the stability of enalapril oral liquid formulations was unpredictable and that only through preparation and testing of formulations could a person of ordinary skill ascertain what combination of ingredients would lead to stable formulations. It would require undue experimentation, including the preparation and testing for 12 months or longer of potentially tens of thousands of enalapril oral liquid formulations, for a person of skill in the art to determine what formulations meet the recited stability requirements and thus fall within the scope of the claims of the ’023 patent.

36. The claims of the ’023 patent are also obvious and therefore invalid under 35 U.S.C. § 103 over the following references, which disclose each element

of the claims of the '023 patent: (1) the 2014 Prescribing Information for the Epaned® Kit; (2) Ip and Brenner, 16 ANALYTICAL PROFILES OF DRUG SUBSTANCES 207, 236 (1987); (3) Raymond C. Rowe et al., HANDBOOK OF PHARMACEUTICAL EXCIPIENTS 605-610 (6th Ed. 2009); (4) U.S. Food and Drug Administration, *Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products* (Nov. 2003, Rev. 2; and (5) U.S. Patent No. 8,568,747 B1. A POSA would be motivated to combine these references to formulate a ready-to-use enalapril liquid formulation that is stable for at least 12 months under refrigerated conditions, to overcome the problems associated with prior art enalapril liquid formulations, such as the Epaned® Kit, including lack of long-term stability. There are no secondary considerations of non-obviousness that have a nexus to the '023 patent claims and that are commensurate in scope with those claims.

37. Bionpharma is entitled to a judicial declaration that the claims of the '023 patent are invalid.

COUNT II
(Declaratory Judgment of Non-Infringement of the '023 Patent)

38. Bionpharma realleges and incorporates by reference the allegations of paragraphs 1-29 as though fully set forth herein.

39. There is an actual, substantial, and continuing case or controversy between Bionpharma and the Azurity regarding, *inter alia*, non-infringement of the claims of the '023 patent.

40. Bionpharma's ANDA, and the manufacture, use, offer for sale, sale, importation, and/or marketing of Bionpharma's ANDA product, has not infringed, does not infringe, and will not infringe, either directly or indirectly, any valid or enforceable claim of the '023 patent, either literally or under the doctrine of equivalents. For instance, any claim from Azurity that Bionpharma's ANDA product infringes the '023 patent are barred on claim preclusion grounds, as such a claim would assert the same cause of action previously litigated and resolved in Bionpharma's favor in connection with *Silvergate Pharmaceuticals, Inc. v. Bionpharma Inc.*, C.A. Nos. 18-1962-LPS, 19-1067-LPS, and 20-1256-LPS (D. Del.). Furthermore, certain claims of the '023 patent require sodium benzoate as a preservative, such as '023 patent claims 17, 18, and 20; Bionpharma's ANDA product does not contain sodium benzoate. Furthermore, Bionpharma has a license to the patents-in-suit under the MMSA, and any patent rights that Azurity may have had in Bionpharma's ANDA have been exhausted and/or extinguished by the first sale doctrine.

41. Bionpharma is entitled to a judicial declaration that the filing of its ANDA, and the manufacture, use, offer for sale, sale, importation, and/or marketing of Bionpharma's ANDA product has not infringed, does not infringe, and will not infringe, either directly or indirectly, any valid or enforceable claim of the '023 patent, either literally or under the doctrine of equivalents.

COUNT III
(Declaratory Judgment of Invalidity of the '405 Patent)

42. Bionpharma realleges and incorporates by reference the allegations of paragraphs 1-29 as though fully set forth herein.

43. There is an actual, substantial, and continuing case or controversy between Bionpharma and the Azurity regarding, *inter alia*, the invalidity of the '405 patent.

44. The claims of the '405 patent are invalid for failure to satisfy one or more of the conditions for patentability in Title 35 of the United States Code, including but not limited, to 35 U.S.C. §§ 101, 102, 103, and/or 112.

45. Claims 1 and 13 of the '405 patent, the only independent claims, recite as follows:

> 1. A stable oral liquid formulation, consisting essentially of: (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
>
> (ii) a preservative, wherein the preservative is sodium benzoate, ascorbic acid, ascorbyl palmitate, BHA, BHT, EDTA and its salts, erythorbic acid, fumaric acid, malic acid, propyl gallate, sodium ascorbate, sodium bisulfate, sodium metabisulfite, sodium sulfite, benzoic acid, potassium sorbate, vanillin, a paraben, or a mixture of parabens; and
>
> (iii) water;
>
> wherein the formulation optionally comprises a buffer to maintain the pH about 4.5 or below, a sweetener, a flavoring agent, or any combination thereof;

wherein the formulation is stable at about 5±3° C. for at least 12 months; and wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

13. A stable oral liquid formulation, consisting essentially of:

(i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;

(ii) a preservative, wherein the preservative is sodium benzoate, ascorbic acid, ascorbyl palmitate, BHA, BHT, EDTA and its salts, erythorbic acid, fumaric acid, malic acid, propyl gallate, sodium ascorbate, sodium bisulfate, sodium metabisulfite, sodium sulfite, benzoic acid, potassium sorbate, vanillin, a paraben, or a mixture of parabens; and

(iii) water;

wherein the formulation optionally comprises a buffer that is present in the formulation at a concentration of up to 20 mM, a sweetener, a flavoring agent, or any combination thereof;

wherein the formulation is stable at about 5±3° C. for at least 12 months; and wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

46. The specification of the ’405 patent does not contain a written description of the subject matter claimed in the ’405 patent, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains to make and use the same. Specifically, nowhere in the specification of the ’405 patent is there any description of an enalapril liquid without a buffer, including an enalapril liquid without a buffer

that would meet the stability limitations recited in the claims. Moreover, Azurity argued during the prosecution history of the '405 patent, and in connection with *Silvergate Pharmaceuticals, Inc. v. Bionpharma, Inc.*, Nos. 18-1062-LPS, 19-1067-LPS, and 20-1256-LPS (D. Del.), that the stability of enalapril oral liquid formulations was unpredictable and that only through preparation and testing of formulations could a person of ordinary skill ascertain what combination of ingredients would lead to stable formulations. There is nothing in the specification of the '405 patent demonstrating to a person of ordinary skill in the art that the named inventors were in possession of the claimed enalapril oral liquid formulations as of the filing date of the application that issued into the '405 patent, and the claims of the '405 patent are therefore invalid for lack of written description.

47. The claims of the '405 patent are also invalid for lack of enablement, as the '405 patent specification does not describe the manner and process of making and using the invention so as to enable a person of skill in the art to make and use the full scope of the invention without undue experimentation. Specifically, nowhere in the specification of the '405 patent is there any data provided or rationale advanced demonstrating that the claimed enalapril oral liquid formulations, some of which do not include buffers, would be stable at refrigerated conditions for the storage periods recited in the claims. Moreover, Azurity argued during the prosecution history of the '405 patent, and in connection with *Silvergate*

Pharmaceuticals, Inc. v. Bionpharma, Inc., Nos. 18-1062-LPS, 19-1067-LPS, and 20-1256-LPS (D. Del.), that the stability of enalapril oral liquid formulations was unpredictable and that only through preparation and testing of formulations could a person of ordinary skill ascertain what combination of ingredients would lead to stable formulations. It would require undue experimentation, including the preparation and testing for 12 months or longer of potentially tens of thousands of enalapril oral liquid formulations, for a person of skill in the art to determine what formulations meet the recited stability requirements and thus fall within the scope of the claims of the '405 patent.

48. The claims of the '405 patent are also obvious and therefore invalid under 35 U.S.C. § 103 over the following references, which disclose each element of the claims of the '405 patent: (1) the 2014 Prescribing Information for the Epaned® Kit; (2) Ip and Brenner, 16 ANALYTICAL PROFILES OF DRUG SUBSTANCES 207, 236 (1987); (3) Raymond C. Rowe et al., HANDBOOK OF PHARMACEUTICAL EXCIPIENTS 605-610 (6th Ed. 2009); (4) U.S. Food and Drug Administration, *Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products* (Nov. 2003, Rev. 2; and (5) U.S. Patent No. 8,568,747 B1. A POSA would be motivated to combine these references to formulate a ready-to-use enalapril liquid formulation that is stable for at least 12 months under refrigerated conditions, to overcome the problems associated with prior art enalapril liquid formulations, such

as the Epaned® Kit, including lack of long-term stability. There are no secondary considerations of non-obviousness that have a nexus to the '405 patent claims and that are commensurate in scope with those claims.

49. Bionpharma is entitled to a judicial declaration that the claims of the '405 patent are invalid.

COUNT IV
(Declaratory Judgment of Non-Infringement of the '405 Patent)

50. Bionpharma realleges and incorporates by reference the allegations of paragraphs 1-29 as though fully set forth herein.

51. There is an actual, substantial, and continuing case or controversy between Bionpharma and the Azurity regarding, *inter alia*, non-infringement of the claims of the '405 patent.

52. Bionpharma's ANDA, and the manufacture, use, offer for sale, sale, importation, and/or marketing of Bionpharma's ANDA product, has not infringed, does not infringe, and will not infringe, either directly or indirectly, any valid or enforceable claim of the '405 patent, either literally or under the doctrine of equivalents. For instance, any claim from Azurity that Bionpharma's ANDA product infringes the '405 patent are barred on claim preclusion grounds, as such a claim would assert the same cause of action previously litigated and resolved in Bionpharma's favor in connection with *Silvergate Pharmaceuticals, Inc. v. Bionpharma Inc.*, C.A. Nos. 18-1962-LPS, 19-1067-LPS, and 20-1256-LPS (D.

Del.). Furthermore, certain claims of the '405 patent require sodium benzoate as a preservative, such as '405 patent claims 9 and 18; Bionpharma's ANDA product does not contain sodium benzoate. Furthermore, Bionpharma has a license to the patents-in-suit under the MMSA, and any patent rights that Azurity may have had in Bionpharma's ANDA have been exhausted and/or extinguished by the first sale doctrine.

53. Bionpharma is entitled to a judicial declaration that the filing of its ANDA, and the manufacture, use, offer for sale, sale, importation, and/or marketing of Bionpharma's ANDA product has not infringed, does not infringe, and will not infringe, either directly or indirectly, any valid or enforceable claim of the '405 patent, either literally or under the doctrine of equivalents.

PRAYER FOR RELIEF

WHEREFORE, Bionpharma respectfully prays for judgment in its favor and against Azurity:

a) Declaring that the claims of the '023 patent are invalid;

b) Declaring that the claims of the '405 patent are invalid;

c) Declaring that the filing of Bionpharma's ANDA, and the manufacture, use, sale, offer for sale, importation, and/or marketing of Bionpharma's ANDA product has not infringed, does not infringe, and will not

infringe, either directly or indirectly, any valid and/or enforceable claim of the ’023 patent either literally or under the doctrine of equivalents;

d) Declaring that the filing of Bionpharma’s ANDA, and the manufacture, use, sale, offer for sale, importation, and/or marketing of Bionpharma’s ANDA product has not infringed, does not infringe, and will not infringe, either directly or indirectly, any valid and/or enforceable claim of the ’405 patent either literally or under the doctrine of equivalents

e) Ordering that Azurity’s Complaint for Patent Infringement be dismissed with prejudice and judgment entered in favor of Bionpharma and CoreRx;

f) Declaring this case exceptional and awarding Bionpharma its reasonable attorneys’ fees and costs under 35 U.S.C. § 285; and

g) Awarding such other and further relief as the Court may deem just and proper.

Dated: [EXHIBIT A]

Respectfully submitted,

CARLTON FIELDS, P.A.

By: [EXHIBIT A]
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EXHIBIT B

M&A DEAL SUMMARY

NovaQuest Capital Management Acquires Azurity Pharmaceuticals

On March 26, 2018, private equity firm NovaQuest Capital Management acquired life science company Azurity Pharmaceuticals, Inc. from Ampersand Capital Partners

Acquisition Highlights

- This is NovaQuest Capital Management's 3rd transaction in the Life Science sector.
- This is NovaQuest Capital Management's 3rd transaction in the United States.
- This is NovaQuest Capital Management's 1st transaction in Massachusetts.

M&A DEAL SUMMARY

Date	**2018-03-26**
Target	**Azurity Pharmaceuticals, Inc.**
Sector	**Life Science**
Buyer(s)	**NovaQuest Capital Management**
Sellers(s)	**Ampersand Capital Partners**
Deal Type	**Secondary Buyout**
Advisor(s)	**TAP Advisors LLC (Financial)**

TARGET

BUYER(S)

1

Buyer	DESCRIPTION
NovaQuest Capital Management	**NovaQuest Capital Management is a private equity firm focused on acquiring and investing in growth-stage middle-market healthcare companies. Specific areas of interest include life science, medical technology, healthcare/facility services, and healthcare focused IT. The Firm targets profitable companies valued up to $500 million with $20 to $100 million of revenue. NovaQuest Capital Management was established in 2000 and is based in Raleigh, North Carolina.**

CATEGORY	Private Equity Firm
FOUNDED	2010
PE ASSETS	3.0B USD
SIZE	Large
TYPE	Sector Focused

Azurity Pharmaceuticals, Inc.

Woburn, Massachusetts, United States

Azurity Pharmaceuticals, Inc. is a privately held, specialty pharmaceutical company focusing on the development and commercialization of value-added proprietary drug products and technologies in the prescription compounding sector of the pharmaceutical industry. The company's product line and development efforts initially are focused on providing optimized, more efficient alternatives for the preparation of the nearly 10 million currently compounded prescriptions, by offering FIRST® Unit-of-Use Prescription Compounding Kits. Use of these branded compounding kits will be beneficial to all triad participants, namely physicians, pharmacists, and patients. Three U.S. patents have been issued to the Company with several additional patents pending.

DEAL STATS	#
Overall	3 of 10
Sector (Life Science)	3 of 6
Type (Secondary Buyout)	1 of 2
State (Massachusetts)	1 of 1
Country (United States)	3 of 9
Year (2018)	2 of 4

PREVIOUS DEAL

DATE	TARGET
2018-01-03	**Viamet Pharmaceuticals, Inc.** Durham, North Carolina, Unite **Viamet Pharmaceuticals, Inc. disco develops breakthrough therapies b leadership in metalloenzyme chemi biology. Company clinical portfolio**

FOLLOWING DEAL

DATE	TARGET
2018-05-14	**Clinical Ink, Inc.** Horsham, Pennsylvania, Unite **Clinical Ink is a clinical technology that offers data certainty from sour submission. The company's Lumer eSource clinical technology and…**

SELLER(S)

SELLER	DESCRIPTION
Ampersand Capital Partners Wellesley, Massachusetts, United States	**Ampersand Capital Partners is a middle-market private equity group that concentrates on growth equity investment opportunities in the healthcare sector. The Firm looks to invest $10 to $100 million in businesses with $10 to $100 million of revenue. Specific areas of interests within healthcare include lab products, specialty diagnostic equipment, pharmaceutical outsourcing, and specialty pharma.**

- & More

7-Day Free Trial

CATEGORY	Growth Capital Firm
FOUNDED	1988
PE ASSETS	2.0B USD
SIZE	Large
TYPE	Sector Focused

Ampersand generally prefers to be the first and sole institutional investor. Ampersand was formed in 1988 and is based in Wellesley, Massachusetts.

DEAL STATS	#
Overall	36 of 44
Sector (Life Science)	14 of 19
Type (Secondary Buyout)	4 of 4
State (Massachusetts)	7 of 9
Country (United States)	36 of 44
Year (2018)	3 of 6

PREVIOUS DEAL

DATE	TARGET	D
2018-03-26	**MedPharm Ltd.** Surrey, United Kingdom **MedPharm Ltd. is a global provider of contract topical and transdermal product design and formulation…**	E

FOLLOWING DEAL

DATE	TARGET
2018-06-01	**Alcami Corp.** Durham, North Carolina, Unite **Alcami Corp. is a world-class fully-integrated end-to-end contract dev and manufacturing organization (C headquartered in North Carolina, w**

Browse

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EXHIBIT C

businesswire
A BERKSHIRE HATHAWAY COMPANY

core Rx - NovaQuest Capital Management

NovaQuest Private Equity Acquires CoreRx, Inc.

New Strategic Financial Sponsor to Support Continued Growth and Capability Expansion

January 19, 2021 06:30 AM Eastern Standard Time

RALEIGH, N.C. & CLEARWATER, Fla.--(BUSINESS WIRE)--NovaQuest Private Equity (“NovaQuest”) today announced its acquisition of CoreRx, Inc. (“CoreRx” or the “Company”), a global contract development and manufacturing organization (“CDMO”).

Based in Clearwater, FL, CoreRx provides clinical and commercial CDMO services to a wide range of small to mid-sized pharmaceutical and biotech clients. Founded in 2006, the Company offers preformulation, formulation, analytical and stability, clinical manufacturing, commercial manufacturing, and packaging services. The Company’s deep development expertise allows it to solve complex formulation challenges. Its small-batch manufacturing capabilities, coupled with a responsive customer mindset, allow CoreRx to be a nimble, hands-on partner for its valued customers.

“This transaction is an endorsement of CoreRx’s success to date and its potential for future growth with NovaQuest, a firm with deep healthcare and life sciences expertise and a long history of partnering with market-leading businesses to take them to the next level,” said Todd R. Daviau, President and CEO of CoreRx. “NovaQuest’s expertise in pharmaceutical services and enabling technologies will be invaluable as we look to further grow and enhance the value of our business in partnership with our customers.”

“Todd and his management team have done an excellent job building CoreRx from the ground up, growing from a small development organization into a high-quality, end-to-end CDMO with proven commercial capabilities,” said Ashton Poole and Jeff Edwards, Partners at NovaQuest. “We look forward to supporting the CoreRx team as they continue to build out their capabilities and provide best-in-class service to the pharmaceutical industry.”

Affiliates of Signet Healthcare Partners, an investor in CoreRx since 2015, will retain a minority position.

Goldman Sachs Specialty Lending Group provided debt financing for the transaction. William Blair & Company served as exclusive financial advisor to CoreRx. Sheppard Mullin and Johnson Pope served as legal advisors to CoreRx, and Smith Anderson served as legal advisor to NovaQuest. Deal terms were not announced.

About CoreRx:

CoreRx is a CDMO with full-service capabilities to support clinical through commercial manufacturing, offering state of the art facilities to support your supply chain needs. Our integrated offerings provide comprehensive services for the development, manufacturing, and testing of solid, liquid, and semi-solid dosage forms. For more information, please visit www.corerxpharma.com.

About NovaQuest Private Equity:

NovaQuest Private Equity is a leading investor in technology and services companies in the life sciences and healthcare sectors. NovaQuest was formed in 2000 with the vision of building an investment platform to provide strategic capital and operational leverage in partnership with strong management teams. The investment team consists of highly seasoned operational and investment professionals with significant investment experience and deep life science and healthcare expertise. Furthermore, NovaQuest benefits from an extensive network of industry experts and relationships that assist in identifying, analyzing and growing NovaQuest portfolio companies and investments. For more information, please visit www.novaquest.com.

Contacts

For further information about CoreRx:
Mark DaFonseca, Chief Business Officer
(727) 259-6950, mark.dafonseca@corerxpharma.com

For media inquiries:
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EXHIBIT E

HOLLAND & KNIGHT LLP
31 West 52nd Street
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Phone: (212) 513-3200
Fax: (212) 385-9010

Attorneys for Plaintiff,
Bionpharma, Inc.

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

BIONPHARMA INC.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	**COMPLAINT**
	)	
CORERX, INC.,	)	
	)	
Defendant.	)	
	)	

Plaintiff Bionpharma Inc. ("Bionpharma"), by way of complaint against defendant CoreRx, Inc. ("CoreRx"), alleges and says:

THE PARTIES

1. Plaintiff Bionpharma is a Delaware corporation with its principal place of business at 600 Alexander Road, Suite 2-4B, Princeton, New Jersey.

2. Defendant CoreRx is a Florida corporation with its principal place of business at 14205 Myerlake Circle, Clearwater, Florida.

JURISDICTION AND VENUE

3. This Court has jurisdiction over this action pursuant to 28 U.S.C. § 1332(a)(1) and 28 U.S.C. § 2201(a). Complete diversity of citizenship exists because this action involves a

dispute between citizens of different states and the amount in controversy, exclusive of interest and costs, exceeds the sum or value of $75,000.

4. This Court has personal jurisdiction over CoreRx at least because CoreRx consented to jurisdiction in this Court (Exhibit A, Section 16.8).

5. Venue is proper based in this district at least because CoreRx consented to venue in this Court (Exhibit A, Section 16.8).

BACKGROUND

6. In November 2020, Bionpharma and CoreRx entered into that certain Master Manufacturing Supply Agreement (the "Agreement") concerning in part terms under which (i) CoreRx is to supply Bionpharma's requirements of enalapril solution (the "Product") generic to the branded product Epaned, and (ii) Bionpharma is to purchase its requirements of the Product from CoreRx (Exhibit A, Section 5.1). A copy of the Agreement, with financial terms and nonpublic information concerning the Product omitted, is annexed hereto as Exhibit A.

7. The purpose of the Agreement is for Bionpharma to acquire Product for resale in the wholesale market for generic pharmaceuticals.

8. Bionpharma holds approved Abbreviated New Drug Application ("ANDA") A212408 for the Product, and commenced selling the Product pursuant to that approval on or about August 17, 2021.

9. Pursuant to 21 U.S.C. § 355(j)(5)(B)(iv), no other ANDA based on Epaned as the reference listed drug may be approved prior to February 13, 2022. Accordingly, at least until that date, Bionpharma enjoys a period during which the Product is the only approved generic to Epaned in the United States.

10. In order to obtain approval of its ANDA for the Product and maintain freedom to

sell the Product, Bionpharma expended and continues to expend significant resources to defeat claims for patent infringement filed against it by Azurity Pharmaceuticals, Inc. ("Azurity"), which holds the marketing authorization for Epaned, and Azurity's predecessor Silvergate Pharmaceuticals, Inc. ("Silvergate").

11. In December 2018, Silvergate (subsequently Azurity) sued Bionpharma in the U.S. District Court for the District of Delaware for infringement of several patents on account of Bionpharma's submission of an ANDA seeking approval to sell the Product. That case went to trial, and on April 27, 2021, the district court ruled that the Product did not infringe the remaining asserted patents. *Silvergate Pharms., Inc. v. Bionpharma Inc.*, C.A., No. 18-1962-LPS (D. Del.), ECF No. 257, Apr. 27, 2021 Op.; *Silvergate Pharms. Inc. v. Bionpharma Inc.*, C.A. No. 19-1067-LPS (D. Del.), ECF No. 244, Apr. 27, 2021 Op.; *Silvergate Pharms., Inc. v. Bionpharma Inc.*, No. CV 18-1962-LPS 2021, WL 1751148 (D. Del., April 29, 2021) (redacted public version of Apr. 27, 2021 Op. in C.A. Nos. 18-1962-LPS and 19-1067-LPS (D. Del.) ("First Wave Suits")). On April 29, 2021, the district court entered final judgment in Bionpharma's favoring the First Wave Suits. *Silvergate Pharms., Inc. v. Bionpharma Inc.*, C.A., No. 18-1962-LPS (D. Del.), ECF No. 270, Final J.; *Silvergate Pharms., Inc. v. Bionpharma Inc.*, C.A., No. 19-1067-LPS (D. Del.), ECF No. 257, Final J. A related action that Azurity filed against Bionpharma on September 18, 2020 involving later-issued patents in the same family—*Silvergate Pharmaceuticals, Inc. v. Bionpharma Inc.*, C.A. No. 20-1256-LPS (D. Del.) ("Second Wave Suit")—was dismissed with prejudice absent a ruling on appeal of the First Wave Suits eliminating collateral estoppel.

12. Having lost the First and Second Wave Suits in Delaware, Azurity decided to try its luck in a different jurisdiction, and filed a new case in June 2021 against Bionpharma in the

U.S. District Court for the District of New Jersey, alleging that sale of the Product would infringe yet another patent. Azurity sought a preliminary injunction, which Bionpharma opposed. Recognizing Azurity's forum shopping, the District of New Jersey granted Bionpharma's motion to transfer the case to the District of Delaware. After the case was transferred, the District of Delaware denied Azurity's motion for a preliminary injunction on November 10, 2021, finding, *inter alia*, that Azurity had not shown a likelihood of success on the merits. *Azurity Pharms., Inc. v. Bionpharma Inc.*, No. 21-cv-01286-LPS (D. Del.), ECF No. 87, Nov. 10, 2021 Oral Order. On October 15, 2021, Azurity filed yet another suit against Bionpharma involving yet another continuation patent. *Azurity Pharms., Inc. v. Bionpharma Inc.*, C.A. No. 21-1455-LPS (D. Del.). Both C.A. Nos. 21-1286-LPS and 21-1455-LPS (D. Del.) ("Third Wave Suits") remain pending.

13. Not content to litigate only against Bionpharma, Azurity in October 2021 also filed two substantially identical suits against CoreRx, alleging that CoreRx's actions in manufacturing the Product for Bionpharma infringed two patents that Azurity was already asserting against Bionpharma in connection with the Third Wave Suits. *Azurity Pharms., Inc. v. CoreRx, Inc.*, 1:21-cv-01522 (D. Del.); *Azurity Pharms., Inc. v. CoreRx, Inc.*, 8:21-cv-02515 (M.D. Fla.).

14. On or about November 26 and 29, 2021, Azurity voluntarily dismissed both of its suits against CoreRx. ECF No. 6, *Azurity Pharms., Inc. v. CoreRx, Inc.*, 1:21-cv-01522 (D. Del.); ECF No. 16, *Azurity Pharms., Inc. v. CoreRx, Inc.*, 8:21-cv-02515 (M.D. Fla.).

15. By virtue of the dismissals of the two cases filed against it by Azurity, CoreRx cannot have a reasonable apprehension that it might face liability to Azurity on account of purported patent infringement arising from CoreRx manufacturing the Product for Bionpharma. FED. R. CIV. P. 41(a)(1)(B).

16. Further, the terms of the Agreement generally provide for indemnification by Bionpharma of CoreRx for claims for patent infringement arising from CoreRx's manufacture of the Product for Bionpharma. (Exhibit A Sections 13.1 and 13.3).

17. On November 30, 2021, CoreRx sent a fax to Bionpharma stating "as of December 1, 2021, CoreRx will be unable to supply enalapril maleate for" the Product. A copy of that notice is annexed hereto as Exhibit B.

18. In response to that fax, Bionpharma requested that CoreRx advise Bionpharma why CoreRx was not able to supply the Product, demanded that CoreRx continue to supply the Product, and gave notice of CoreRx's breach of the Agreement. A copy of Bionpharma's correspondence to CoreRx is annexed hereto as Exhibit C.

19. On or about August 26, 2021, Bionpharma had placed an order with CoreRx for a quantity of Product in accordance with the forecasts provided to CoreRx. A copy of the order, with financial terms and nonpublic information concerning the Product omitted, is annexed hereto as Exhibit D.

20. The order referred to in paragraph 19 above is a Firm Order pursuant to the Agreement (Exhibit A Section 5.3), and complies with all contractual formalities and requirements.

21. CoreRx has manufactured and Bionpharma has taken possession of approximately 30% of the ordered Product from the order referred to in paragraph 19. The balance remains outstanding. These bottles of Product had been scheduled to be shipped by CoreRx to Bionpharma on December 28, 2021.

22. In addition to the correspondence in Exhibit B, CoreRx has advised Bionpharma that it will not manufacture and ship to Bionpharma the remaining approximately bottles of

Product that are the subject of the Firm Order.

23. Upon information and belief, based on the following, CoreRx procured its purported inability to supply Product to Bionpharma through an agreement with Azurity, which is now a sister company of CoreRx under private equity control:

a. In or around January 2021, CoreRx was purchased by Novaquest Investment Management or an affiliate ("Novaquest").

b. Novaquest also owns Azurity.

c. Of the seven members of the board of directors of CoreRx, five are also on the board of directors of Azurity (the "Overlapping Directors"), and several also have positions at Novaquest:

1. Frank Leo – board member of CoreRx; chairman of the board of Azurity.

2. Nailesh Bhatt – board member of CoreRx; board member of Azurity.

3. Jeff Edwards – board member of CoreRx; board member of Azurity; founder and investment committee member of Novaquest.

4. Ashton Poole – board member of CoreRx; board member of Azurity; partner at Novaquest.

5. Vern Davenport – board member of CoreRx; board member of Azurity; partner and member of the private equity investment committee at Novaquest.

d. The five Overlapping Directors named above also constitute a majority of the seven-member board of Azurity.

e. In addition to the Overlapping Directors, Ajay Damani, who became CEO and a board member of CoreRx in October 2021, was immediately prior to that a Strategic Advisor with Novaquest.

f. The fax from CoreRx to Bionpharma stating that CoreRx would no longer supply Product to Bionpharma was sent on November 30, 2021, *i.e.*, one day after the dismissal of the second suit against CoreRx by Azurity, which was filed on November 26, 2021, suggesting a connection between dismissal of Azurity's complaints against CoreRx and CoreRx's refusal to continue supplying Bionpharma.

g. On December 7, 2021, Azurity filed a letter in one of the Third Wave Suits against Bionpharma (21-1286-LPS (D. Del.)) stating that "Azurity's dismissals against CoreRx Inc., Bionpharma's manufacturer, were resolved and dismissed by mutual agreement." A copy of the letter is annexed hereto as Exhibit E.

h. The cessation of generic competition for Epaned resulting from CoreRx's refusal to supply Product to Bionpharma directly benefits Azurity, which is related to CoreRx through Novaquest.

i. Other than seeking to benefit its related company Azurity, there is no apparent economic or business reason for CoreRx to discontinue supply of Product to Bionpharma under the Agreement.

j. On or about November 19, 2021, CoreRx complained to Bionpharma that the price it had negotiated for supply of Product in the Agreement was too low, and that it wanted Bionpharma to agree to a substantial price increase, even

though the price in the Agreement had been negotiated just one year ago, and even though the costs of materials and manufacturing had not substantially increased between the time the Agreement was entered into in November 2020 and CoreRx's demand for a price increase in November 2021.

k. CoreRx has refused to tell Bionpharma the reason why it is purportedly unable to continue supply of Product to Bionpharma under the Agreement.

l. CoreRx has not experienced a Force Majeure Event under the Agreement (Exhibit A Section 16.9).

COUNT 1 – BREACH OF CONTRACT

24. Bionpharma incorporates all prior allegations as if set forth fully herein.

25. Bionpharma has performed its obligations under the Agreement.

26. By refusing to supply Product to Bionpharma under the terms set forth in the Agreement, CoreRx has breached and is in breach of the Agreement.

27. Bionpharma will suffer damages on account of CoreRx's breach of the Agreement.

28. Manufacture and sale of the Product is subject to and regulated under the federal Food, Drug & Cosmetic Act, and implementing regulations adopted by the U.S. Food & Administration.

29. Given that CoreRx gave Bionpharma only one day notice that CoreRx would not continue to supply Product under the Agreement, Bionpharma cannot secure an alternate supplier of Product before it exhausts the inventory of Product it has on hand.

30. If CoreRx does not continue to supply Product under the Agreement until Bionpharma is able to secure an alternate supplier, Bionpharma will suffer irreparable injury.

COUNT 2 – DECLARATORY JUDGMENT

31. Bionpharma incorporates all prior allegations as if set forth fully herein.

32. By virtue of the foregoing, there is an actual and present controversy between Bionpharma and CoreRx that is amenable to resolution by declaratory judgment.

PRAYER FOR RELIEF

WHEREFORE, plaintiff Bionpharma demands judgment against defendant CoreRx as follows:

A. For injunctive relief compelling CoreRx to continue to supply Product for the duration of the Agreement under the terms thereof, or at least until Bionpharma is able to arrange for, and secure sufficient quantities of Product from an alternate supplier.

B. Declaring that CoreRx is in breach of the Agreement, and that it is required to continue to supply Product for the duration of the Agreement under the terms thereof.

C. Awarding Bionpharma its actual damages.

D. Awarding costs of suit and reasonable attorneys' fees.

E. Awarding such other and further relief as may be appropriate.

DATED: December 13, 2021

HOLLAND & KNIGHT LLP

By: */s/ Charles A. Weiss*

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Attorneys for Plaintiff, Bionpharma, Inc.

Exhibit A

EXECUTION VERSION

MASTER MANUFACTURING SUPPLY AGREEMENT

This **Master Manufacturing Supply Agreement** (this **"Agreement"**) is hereby entered into as of November __, 2020 (the **"Effective Date"**) by and arch between CoreRx, Inc., a Florida corporation**,** with offices located at 14205 Myerlake Circle, Clearwater FL 33760 and its Affiliates, (collectively, **"CoreRx"**) and Bionpharma Inc., (**"Bion"**), a Delaware corporation, having its principal place of business at 600 Alexander Road, Suite 2-4B, Princeton, NJ 08540 (each, a **"Party"** and collectively, the **"Parties"**).

Background

Bion is in the business of commercializing various generic pharmaceutical products. CoreRx has experience in manufacture and supply of Products.

NOW THEREFORE, in consideration of the mutual promises, covenants and agreements hereinafter set forth and for good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, Bion and CoreRx hereby agree as follows:

ARTICLE 1. DEFINITIONS

1.1 Defined Terms. Capitalized terms used in this Agreement and not otherwise defined herein shall have the meaning set forth below:

"Affiliate(s)" means as to a Party, any party which controls, is controlled by, or is under common control with such Party. For purposes of the foregoing definition, the term "control" (including with correlative meaning, the terms "controlling", "controlled by", and "under common control with") as used with respect to any applicable party, shall mean the possession, directly or indirectly, of the power to direct or cause the direction of the management and policies of such party, whether through ownership of equity, securities, or partnership interest or by contract, or otherwise. Ownership of more than fifty percent (50%) of the securities or other ownership interests representing the equity, the voting stock or general partnership interest in an entity, or greater than fifty percent (50%) interest in the income of such corporation or other business entity shall, without limitation, be deemed to be control for purpose of this definition.

"ANDA" means an Abbreviated New Drug Application prepared in conformance with applicable FDA regulations for filing with the FDA for marketing authorization of a given Product.

"Agency" means any applicable local, national or supranational government regulatory authority involved in granting approvals and/or exercising authority with respect to the manufacture of a pharmaceutical product in the Territory, including in the FDA.

"API" means the active pharmaceutical ingredient and related substance or substance combination used in manufacturing the Product.

"Applicable Laws" means all laws, rules, regulations and guidelines of any Governmental Authority with jurisdiction over the development, manufacturing, exportation, importation, promotion, marketing, sale or distribution of the Product and/or the performance of a Party's obligations under this Agreement, to the extent applicable and relevant, and including specifically, but without limitation, the FD&C Act, all cGMP and current Good Clinical Practices or similar standards or guidelines of the FDA and including trade association guidelines, where applicable, as well as U.S. export control laws and the U.S. Foreign Corrupt Practices Act.

"Batch" means the Product that results from a single Manufacturing process, inclusive of Material.

"Bion Intellectual Property" means Know-How, including Bion Improvements, that is owned or Controlled by Bion or its Affiliates during the term of this Agreement and that is necessary for or directly related to the Manufacture, use, sale, offering for sale or importing of the Products, including any tangible materials that are provided by Bion to CoreRx for use in the conduct of any Program. The term Bion Intellectual Property does not include any Know-How, which is, as of the Effective Date or later becomes, generally available to the public, excluding Bion Confidential Information or Know-How owned or Controlled by Bion that is publicly disclosed by a Third Party without the consent of Bion, and Know-How included in Bion Patent Rights.

"Bion Patent Rights" means those Patent Rights that Cover Bion Intellectual Property and are Controlled by Bion at any time during the term of this Agreement.

"Business Day" means any day other than a Saturday, a Sunday, or a national holiday in the United States.

"Business Failure" means (i) an actual failure of CoreRx (or any of its Affiliates) to pay its (or their respective) employees or vendors, or to meet its (or their respective) other financial obligations, (ii) a determination by Bion (in its reasonable belief) that CoreRx (or any of its Affiliates) may be unable to pay its (or their respective) employees or vendors, or to meet its (or their respective) other financial obligations, and CoreRx's failure to provide assurances (within thirty (30) days after written notice thereof by Bion) reasonably satisfactory to Bion that CoreRx (and its Affiliates) will be able to make such payments and meet such obligations, (iii) CoreRx (or any of its Affiliates) becoming the subject of any voluntary or involuntary receivership proceeding, bankruptcy, insolvency, liquidation, or assignment for the benefit of creditors, (iv) a determination by Bion (in its reasonable belief) that CoreRx (or any of its Affiliates) may become the subject of any voluntary or involuntary receivership proceeding, bankruptcy, insolvency, liquidation, or assignment for the benefit of creditors, and CoreRx's failure to provide assurances (within thirty (30) days after written notice thereof by Bion) reasonably satisfactory to Bion that any such proceeding or action will not occur, or (v) a determination by Bion (in its reasonable belief) that CoreRx may be unable to satisfy any of its obligations under this Agreement (which may be based on actual or perceived risks, including performance risks, ethical risks, financial solvency risks or other risks); in each case of any of the foregoing, even if as a result of Force Majeure.

"cGMP" means current good manufacturing practices as set forth in 21 C.F.R. §§ 210 and 211, or any Applicable Law, similar regulations, guides, guidances or directives, as amended from time to time.

"Commercialize" or **"Commercialization"** means the commercial exploitation of a Product through (i) manufacturing and selling the Product, (ii) assigning or licensing some or all the commercial rights to the Product to third parties, (iii) entering into a joint venture, partnership or other business arrangement regarding the manufacture, marketing and/or sale of the Product, or (iv) some other agreement or arrangement to produce revenue from the Product.

"Commercially Reasonable Efforts" means, with respect to each Party, the efforts and commitment of resources in accordance with such Party's reasonable business, legal, medical, and scientific judgment that are consistent with the efforts and resources such Party uses for other Product owned by it or to which it has exclusive rights, which are of similar market potential and at a similar stage in their life cycle, taking into account the competitiveness of the marketplace, the regulatory structure involved, the profitability of the applicable Product and other relevant factors, including technical, legal, scientific, medical, sales performance, and/or marketing factors. The term "Commercially Reasonable" shall have correlative meaning.

"Confidential Information" means all non-public information of any kind whatsoever (including without limitation, data, materials, compilations, formulae, models, patent disclosures, procedures, processes, projections, protocols, results of experimentation and testing, specifications, strategies,

techniques and all non-public Intellectual Property and Know-How), and all tangible and intangible embodiments thereof of any kind whatsoever (including without limitation, materials, samples, apparatus, compositions, documents, drawings, machinery, patent applications, records and reports), which are disclosed by either party to the other Party including any and all copies, replication or embodiments thereof. The terms, subject matter and substance of this Agreement shall be deemed the Confidential Information of both Parties. Confidential Information shall not include information which: (a) is known to the receiving Party, as evidenced by the receiving Party's prior written records, before receipt thereof under this Agreement; (b) is disclosed to the receiving Party by a third person who is under no obligation of confidentiality to the disclosing Party hereunder with respect to such information and who otherwise has a right to make such disclosure; (c) is or becomes generally known in the public domain through no fault of the receiving Party; or (d) is independently developed by the receiving Party, as evidenced by the receiving Party's written records, without access to such information

"Control" or "Controlled" means, with respect to any information, intellectual property right or Regulatory Approval, possession by a party of the ability (whether by ownership, license or otherwise) to grant access, rights, title, possession, a license or a sublicense, as applicable, to such intellectual property right without violating the terms of any Third Party agreement, court order, or other arrangement or legal obligation.

"CoreRx Equipment" means all equipment and machinery used to (or otherwise necessary for), directly or indirectly, Manufacture Product,

"CoreRx Intellectual Property" means Know-How that is owned or Controlled by CoreRx or its Affiliates during the term of this Agreement and that is related to the Manufacture, use, sale, offering for sale or importing of the Products, including any tangible materials that are provided by CoreRx to CoreRx for use in the conduct of any Program. The term CoreRx Intellectual Property does not include any Know-How, which is, as of the Effective Date or later becomes, generally available to the public, excluding CoreRx Confidential Information or Know-How owned or Controlled by CoreRx that is publicly disclosed by a Third Party without the consent of CoreRx, and Know-How included in CoreRx Patent Rights.

"**CoreRx Patent Rights"** means those Patent Rights that Cover CoreRx Intellectual Property and are Controlled by CoreRx at any time during the term of this Agreement.

"Cover" means (a) with respect to a granted patent, a Valid Claim thereof would be infringed in the absence of a right, authorization, consent or license with respect to such claimed subject matter, or (b) with respect to a patent application that has not been granted, a Valid Claim thereof, that if granted, would be infringed in the absence of a right, authorization, consent or license with respect to such claimed subject matter.

"Delivery" or **"Deliver"** or **"Delivered"** means CoreRx's delivery of Product in accordance with the Delivery Terms.

"Delivery Address" means, with respect to a given order of Product, the address where the quantities of Product under such order are to be shipped, as set forth in the applicable order.

"Delivery Date" means the date by which Bion shall take delivery of Product as set forth in a Firm Order.

"Delivery Terms" means, with respect to a given Product, the delivery terms (based on Incoterms 2010) for the delivery of such Product. Unless otherwise set forth in the Addendum for a given Product, the "Delivery Terms" for each Product shall be FCA the Delivery Address.

"Dollar" means the United States dollar.

"DMF" means the drug master file as described in 21 C.F.R. §314.420 containing detailed information concerning the synthesis, manufacture, analysis and stability of the API as required for the manufacture, importation, marketing and sale of the Product in the Territory.

"Drug Product" means a drug product as defined in 21 C.F.R. §314.3 for administration to human subjects.

"Facility" means with respect to a given Product, (a) CoreRx's M-1 facility located at 14205 Myerlake Circle, Clearwater, FL 33760 and/or M-2 facility located at 5777 Myerlake Circle, Clearwater FL 33760, and/or M-3 facility located at 5733 Myerlake Circle, Clearwater, FL 33760, as well as (b) such other facility where such Product may be Manufactured as approved by Bion in writing pursuant to Section 3.7.

"FDA" means the United States Food and Drug Administration or any successor agency thereto.

"FD&C Act" means the Food, Drug & Cosmetic Act of 1938 and applicable regulations promulgated thereunder, as amended from time to time.

"Firm Order" means a purchase order for a given Product issued by Bion (and/or its Affiliate, as applicable) under this Agreement and the relevant Addendum. Each Firm Order shall specify the quantity of Product ordered, the pack size, the required Delivery Date, and the Delivery Address (as well as any specific shipping instructions, if applicable), in each instance in accordance with this Agreement.

"First Commercial Sale" means the means the first transfer for value in an arms-length transaction to a Third Party distributor, agent or end user in a country within the Territory after obtaining all Regulatory Approvals necessary for such transfer in such country.

"GAAP" means United States Generally Accepted Accounting Principles in effect from time to time, consistently applied.

"Governmental Authority" means any court, tribunal, arbitrator, agency, legislative body, commission, official or other instrumentality of (i) any government of any country, or (ii) a federal, state, province, county, city or other political, administrative or regulatory subdivision thereof.

"Know-How" means, with respect to a given Product, proprietary information concerning: manufacturing protocols and methods, Product formulations, product specifications, processes, product designs, plans, trade secrets, ideas, concepts, manufacturing information, engineering and other manuals and drawings, standard operating procedures, flow diagrams, chemical, pharmacological, toxicological, pharmaceutical, physical and analytical, safety, quality assurance, preclinical data, quality control and clinical data, technical information, and research records.

"Label," "Labeled" or **"Labeling"** shall refer to such labels and other written, printed or graphic matter, (i) upon a Product or any container or wrapper utilized with the Product, or (ii) accompanying a Product, including without limitation, package inserts.

"Latent Defect" means any deficiency (including any Product that fails to meet the representations, warranties or other quality requirements set forth in this Agreement) that was not discovered by Bion upon a reasonable inspection of the Product (based on physical inspection, identity test and review of the certificate of analysis).

"Losses*"* means any and all liabilities, losses, fines (including criminal, administrative and civil fines), costs, damages or expenses, including reasonable attorneys' fees.

"Manufacture" or **"Manufacturing"** or **"Manufactured"** means, with respect to a given Product, all operations performed by CoreRx for the manufacture and commercial supply of such Product hereunder, including, as applicable, receipt (including testing) and storage of Materials, production, formulation, filling, visual inspection, packaging, labeling, handling, warehousing, quality control testing (including in-process, initial release and stability testing), release, as applicable, and shipping of Product, and also including such activities as may be specified in the ANDA approval and master batch records

"Materials" means all raw materials, including API, components (including packaging materials), and

other potential product-contacting items necessary for, or otherwise used in, the Manufacture of Product hereunder, as applicable.

"Minimum Remaining Percentage" means, with respect to a given Product, the minimum percentage of the maximum shelf-life for such Product that is required to be remaining at the time of Delivery of such Product hereunder, which shall in all cases be ninety (90%).

"Orange Book" means the *Approved Drug Product with Therapeutic Equivalence Evaluations* published by the FDA, as amended.

"Overhead" means all customary and usual operating expenses directly related to the Product incurred by and in support of the particular manufacturing cost centers, purchasing department and quality assurance operations, related to the Product (including labor, related payroll taxes and employee benefits), depreciation, general taxes, rent, repairs and maintenance, supplies, utilities and factory administrative expense.

"Packaging" means all primary containers, including bottles, cartons, shipping cases or any other like matter used in packaging or accompanying a Product.

"Patent Rights" means patents and patent applications, divisionals, continuations, continuations-in-part, reissues, extensions, supplementary protection certificates and foreign counterparts thereof.

"Person" means an individual, corporation, partnership, limited liability company, firm, association, joint venture, estate, trust, governmental or administrative body or agency, or any other entity.

"Pharmacovigilance Expenses**"** means expenses related to managing and administering to safety reporting system and its related activities for the sale of pharmaceutical products in the Territory as required by Applicable Law.

"Proceedings" means, without limitation, governmental, judicial, administrative or adversarial proceedings (public or private), litigation, suits, arbitration, disputes, claims, causes of action or investigations.

"Product" or **"Products"** means the particular Products to be supplied hereunder. Product supplied hereunder in liquid, powder or semi-solid form will be provided in final finished packaged form ready for marketing, distribution and sale or other use and Product supplied hereunder in capsule or tablet form will be provided in bulk format. For clarity, unless the context otherwise requires, references to "Product" in this Agreement shall be construed to refer to each given Product hereunder (and thus understood to mean a given Product on a "Product-by-Product" basis); provided, that to the extent the term "Product" is used more than one time in a given provision herein, the first such reference shall be understood to mean "a given Product" and each successive reference shall be understood to mean "such Product".

"Quality Agreement" means that certain quality agreement to be executed by the Parties (or their respective Affiliates) setting out the roles and responsibilities related to the Manufacturing of Product, as such agreement may be amended from time to time by the Parties.

"Reference Product" means all approved strengths and dosage forms that are approved for sale of the reference listed brand Drug Product, listed in the Orange Book or other relevant database of the FDA.

"Regulatory Approval" means the applicable approvals necessary to make Product, including applications submitted to the FDA, and all applicable product and/or establishment licenses, registrations, permits or other authorizations as may be necessary in connection with the applicable Product, and which are necessary for the commercial manufacture, commercialization, use, storage, importation, transport, promotion, pricing, distribution or sale of such Product in the Territory, including, without limitation, an ANDA

"SDE Agreement" means a safety data exchange agreement to be entered into by the Parties which addresses pharmacovigilance matters.

"Specifications" means, with respect to a given Product, the then most current specifications for both the API and the Product established by CoreRx and approved by Bion, as set forth in any applicable application for Regulatory Approval, or prior to the application, as embodied in applicable documents leading up to such application (e.g., in connection with a bioequivalence study), or as may be superseded in the future by an applicable Regulatory Approval for such a Product, including (as applicable) any supplements or amendments thereof and statements of pharmaceutical manufacturing, filling, storage and quality control procedures, submission batch specifications, and Labeling and Packaging specifications (as such may be revised from time to time in accordance with Applicable Laws) together with any additional specifications that may be agreed to between the Parties.

"Territory" means the United States, its territories and possessions including, without limitation, Puerto Rico and the District of Columbia.

"Therapeutic Equivalent" means a Drug Product that is therapeutically equivalent (as such term is defined in the Orange Book) to the Reference Product.

"Third Party" or **"Third Parties"** means any Person or entity other than a Party or its Affiliates.

"Third Party Claim" means any claim, demand, proceeding, action or cause of action by a Third Party.

"Transfer Price" means the price agreed by the Parties for a Product as specified in Attachment 2 hereof, and mutually amended from time to time by electronic email or other written format.

"Validation" or **"Validating**" or "**Validated**" means documented evidence that provides a high degree of assurance that the Manufacturing process controls are adequate to consistently produce a Product, in accordance with cGMPs and Bion Intellectual Property, and that meets the Product Specifications.

"Valid Claim" means a claim of (a) a granted patent which has not been disclaimed, abandoned or surrendered or declared invalid or unenforceable in a final, unappealable or unappealed decision of a judicial or administrative court, government agency or patent office of appropriate jurisdiction, or (b) a patent application which has not been formally terminated or abandoned, without right of appeal, without issuance of a patent, or has not been in active prosecution for more than five (5) years without issuance of a patent.

"Violation" means that either CoreRx, or any of its officers, directors, or subcontractors has been: (a) convicted of any of the felonies identified among the exclusion authorities listed on the U.S. Department of Health and Human Services, Office of Inspector General website, including 42 U.S.C. 1320a-7(a) (https://oig.hhs.gov/exclusions/authorities.asp); (b) identified in the OIG List of Excluded Individuals/Entities (LEIE) database (https://oig.hhs.gov/exclusions/index.asp) on said website or the U.S. General Services Administration's list of Parties Excluded from Federal Programs (http://www.sam.gov); or (c) listed by any US Federal agency as being suspended, debarred, excluded, or otherwise ineligible to participate in Federal procurement or non-Procurement programs, including under 21 U.S.C. 335a (http://www.fda.gov/ora/compliance_ref/debar/) (each of (a), (b) and (c) collectively the "**Exclusions Lists**").

"Waste" means any waste material, pollutant, contaminant, toxin, carcinogen, biohazard, radioactive or hazardous gaseous, liquid or solid material of any kind or any other waste that may or could pose a hazard to the environment or human health or safety, including any routine process waste or any by-product, arising from Manufacture of Product, including petroleum, petroleum hydrocarbons, petroleum products or petroleum by-products, radioactive materials, asbestos or asbestos-containing materials, gasoline, diesel fuel, pesticides, radon, urea formaldehyde, mold, lead or lead-containing materials, polychlorinated biphenyls and any other chemicals, materials, substances or wastes in any amount or concentration which are now or hereafter become defined as or included in the definition of

"hazardous substances", "hazardous materials", "hazardous wastes", "extremely hazardous wastes", "restricted hazardous wastes", "toxic substances", "toxic pollutants", "pollutants", "regulated substances", "solid wastes", or "contaminants" or words of similar import under Applicable Laws.

1.2 Other Defined Terms. The following terms shall have the meanings set forth in the section appearing opposite such term:

"Agreement"	Preamble
"Approved Manufacturer"	Section 5.14
"Bion"	Preamble
"Bion Improvements"	Section 10.4
"Bion Parties"	Section 13.2
"Continuous Improvement Program"	Section 6.4
"CoreRx"	Preamble
"CoreRx Parties"	Section 13.1
"Data Set"	Section 7.14
"Deficiency"	Section 12.3
"Dispute"	Section 16.7
"Effective Date"	Preamble
"Force Majeure Event"	Section 16.9
"Offer Notice"	Section 15.1
"Party(ies)"	Preamble
"Supply Interruption"	Section 5.11
"Taxes"	Section 6.8.

ARTICLE 2. MASTER AGREEMENT; SCOPE OF WORK; DEVELOPMENT

2.1 Master Agreement. This Agreement establishes the general terms and conditions applicable to CoreRx's Manufacture and supply of the Product hereunder and the performance of activities under this Agreement with respect to the Product hereunder.ARTICLE 3. FACILITY AND EQUIPMENT

3.1 Implementation. CoreRx will design the layout of the portion of the Facility used to Manufacture Products and equip the production line(s) for the Products located at the Facility in accordance with a jointly agreed plan and schedule as may be necessary to deliver a production line that meets the specifications for the production line and the Facility that are established by mutual agreement of the Parties. CoreRx shall not change the specifications for the production line specifications without consulting Bion. On not less than seven days' notice to CoreRx, Bion will have the right to inspect the progress of work at the Facility relating to the performance of this Agreement at all reasonable times during the implementation process and to confer with CoreRx to confirm compliance with the agreed specifications for the production line(s) for the Products, and Bion will be consulted concerning any matters that could cause a delay in completion of the production line(s) at the Facility. Bion and CoreRx will, from time to time during the implementation process, confer regarding the quality standards for the layout of the production line operations.

3.2 Maintenance and Operation. CoreRx agrees, at its own cost, to maintain and operate the Facility, and the CoreRx Equipment used directly or indirectly to Manufacture Product, in an acceptable state of repair and operating efficiency, and in accordance with Applicable Law (including cGMPs) all applicable Bion Intellectual Property and all applicable Agency requirements.

3.3 Qualification and Validation. CoreRx, at its cost, shall be responsible for Validating the CoreRx Equipment (including conducting installation, operational and performance qualification), production, cleaning, packaging, process and any other appropriate steps performed at the Facility in accordance with the Bion Intellectual Property and as required by, and in accordance with, the Applicable Laws (including cGMPs); Validation procedures used by CoreRx immediately prior to the Effective Date may be used; provided that such procedures (i) are found to be acceptable to Bion, (ii)

meet applicable regulatory requirements and (iii) are found acceptable by Agency inspectors, if applicable. If Bion or any Agency finds CoreRx's Validation procedures to be unacceptable, then all Validation must be repeated to meet the criteria given in the Bion Intellectual Property and all applicable regulatory requirements and guidelines and to receive all Agency and Bion approvals. Notwithstanding the foregoing, if Bion reasonably finds, or any Agency finds, CoreRx's validation or qualification procedures to be unacceptable, then all validation or qualification must be repeated to meet the criteria given in the cGMPs and Bion Intellectual Property and, as applicable, to the satisfaction of the Agency or Bion, as applicable. CoreRx shall ensure the cleanliness of the equipment, using a cleaning validation procedure that complies with FDA requirements, prior to Manufacturing Product.

3.4 Equipment Problem. CoreRx agrees that in the event that either CoreRx Equipment is inoperable and such inoperation is expected to result in a delay of supply of Product to Bion, CoreRx shall notify Bion immediately in writing of such problem and CoreRx shall work to expeditiously rectify any such problems. CoreRx will inform Bion immediately if Delivery of any Firm Order will be delayed. With respect to all CoreRx Equipment, CoreRx shall be responsible for the costs of all maintenance and repairs, including all spare parts.

3.5 Changes and Change Control.

3.5.1 Notwithstanding anything herein to the contrary or in the Quality Agreement, except as otherwise agreed to by Bion in writing or as may be required to comply with the Applicable Laws (including cGMPs), CoreRx shall not amend, change, or supplement any of the following without Bion's prior written consent: (1) the Product Specifications; (2) the Materials; (3) the specifications for Materials that have regulatory impact (e.g., specification is listed in the regulatory filing) or the potential for quality impact on the Products; (4) the source of Materials that have regulatory impact (e.g., supplier is listed in the regulatory filing) or the potential for quality impact on the Products; (5) the Bion Intellectual Property or CoreRx Intellectual Property; (6) the equipment and machinery, other than in-kind replacements, used in the Manufacture of Product that have a direct impact on the quality of the Product; (7) the test methods used in connection with the Manufacturing of Product that have regulatory impact (e.g., method is listed in the regulatory filing) or the potential for quality impact on the Products; (8) the process for Manufacturing Product or Materials; (9) the cleaning process or procedures used at any time on the equipment and machinery used in the Manufacture of Products; and/or (10) any DMF for a Product.

3.5.2 Any change in any of the foregoing shall, in each instance, comply with the Applicable Laws (including cGMPs) and shall be made in accordance with the Quality Agreement. In the event that CoreRx is required to change any of the foregoing in order to comply with the Applicable Laws (including cGMPs) or such change is otherwise agreed to by Bion in writing, CoreRx shall: (x) immediately notify Bion of such change and use commercially reasonable efforts to implement such change as soon as reasonably practicable; (y) be responsible, at its expense, for ensuring that all Product Manufactured following such change meets the Product Specifications and the Product quality and yields achieved during the validation batches; and (z) provide Bion with all information with respect to the Manufacture of the Product in connection with such change needed to amend any regulatory filings (including ANDAs) maintained with respect to the subject Product. To the extent permitted by Applicable Laws, CoreRx shall continue to supply Bion with Product approved under any applicable existing DMF and/or Bion's existing regulatory filings (including ANDAs), as applicable, for the subject Product until such time as the Product Manufactured following such change is permitted under the amended regulatory filings therefor. In the event that CoreRx intends to change any of the foregoing, Bion shall work in a timely fashion to provide any required response to CoreRx.

3.5.3 Prior to implementing any such change, the Parties shall agree on the reasonable costs thereof; provided that CoreRx shall use commercially reasonable efforts to mitigate the costs thereof. Notwithstanding the foregoing, (i) if the change is required by Applicable Laws and such required change benefits the Manufacture of the Product, as well as the manufacture of other products by CoreRx at the Facility, then Bion shall be responsible for reimbursing CoreRx for a proportionate share of the

costs (based on the relative benefits to the Products hereunder and the benefits to such other CoreRx products taking into account the remaining duration of the Term), and in the event that the Parties disagree as to such costs or such proportionate share, the matter shall be resolved in accordance with Section 16.7 (and in making its determination the Parties shall take into account the remaining duration of the Term) and (ii) in all other cases, CoreRx shall bear all costs of such change.

3.6 Discretionary Changes. In the event that either Party desires to propose discretionary changes (i.e., changes which are not required by cGMPs or other Applicable Laws) during the Term to the Product Specifications or to the Manufacturing process (in each case, which discretionary changes would otherwise require consent as set forth in Section 3.6.1), the Parties shall discuss such discretionary changes and any Manufacturing issues identified by either Party in connection with implementing such change. In all cases, such discretionary changes shall be made in accordance with any change control procedures in the Quality Agreement to the extent applicable. The provisions of Sections 3.6.2 and 3.6.3 shall apply with respect to implementing any such discretionary change. Notwithstanding the foregoing, in all cases, the Product Specifications may be amended or supplemented from time to time by Bion upon written notice to CoreRx in accordance with any change control procedures in the Quality Agreement.

3.7 Manufacturing at Facility. CoreRx shall Manufacture all Product supplied hereunder at the Facility. Manufacturing of Product may not be relocated from the Facility without Bion's prior written consent (it its sole discretion). Any such relocation of the Manufacturing of a given Product shall comply with the Applicable Laws (including cGMPs) and shall be made in accordance with Sections 3.6.2 and 3.6.3, and the Quality Agreement, to the extent applicable. Without limiting the foregoing, in the event that CoreRx desires to relocate the Manufacturing of any Product, in connection with such relocation, the Parties shall discuss any amendments to this Agreement as reasonably requested by Bion or the CoreRx (as the case may be), including with respect to (i) the Delivery Terms, (ii) provisions related to transfer of title, in each case, to take into account the relocation of such activities, and (iii) the procedures to be followed to secure any Regulatory Approvals required by in connection with such relocation. CoreRx shall be responsible for the costs of any relocation and any Product cost increase in connection with such relocation.

3.9 Manufacture of Product. For the avoidance of doubt, each change referred to in Section 3.5 or Section 3.6 or Section 3.7 shall be agreed to by the Parties (to the extent such agreement is required pursuant to Section 3.5 or Section 3.6 or Section 3.7), as applicable, including the implementation date of any such change, only as it applies to Manufacturing of Product.

3.10 Storage. CoreRx shall, in accordance with the Applicable Laws (including cGMPs), Bion Intellectual Property, and Product Specifications, maintain adequate storage accommodations for all of the Materials, Product and any other materials or products reasonably requested by Bion. CoreRx shall notify Bion immediately whenever the inventories of Materials become insufficient to Manufacture the Product to meet the Delivery Date(s). Products that have been quality control released by CoreRx shall be stored by CoreRx in separate segregated area until Delivered.

3.11 Waste. In connection with the Manufacture of Product hereunder, CoreRx shall be solely responsible for maintaining safety procedures in connection with the Manufacture of Product and for the generation, treatment, storage and/or disposal of Waste relating thereto, all of which shall comply with all Applicable Laws, including all applicable environmental and occupational safety and health requirements in the jurisdiction of the Facility. At the request of Bion, CoreRx shall provide a Certificate of Destruction to Bion upon completion of disposal of any Waste.

ARTICLE 4. MATERIALS

4.1 Materials. CoreRx shall be responsible for procuring all Materials in adequate quantities to Manufacture each Product. CoreRx shall purchase adequate quantities of the Materials. Bion and CoreRx shall be responsible for negotiating the price for such Materials. For clarity, the Transfer Price already takes into account the costs of Materials, and Bion shall not be liable to CoreRx for any

increases in the cost of such Materials except as provided in Section 6.2.

4.2 API Supply. With respect to API for each Product, CoreRx shall take actions to ensure that all API supplied by the API manufacturer is manufactured in accordance with cGMP and all Applicable Laws and that the manufacturer has a successful history in satisfying all FDA requirement at the facility supplying the API; that the API is consistent with the applicable Product Specifications and Regulatory Approval (or associated application prior to approval) and is in compliance with applicable compendial (e.g. United States pharmacopeia) specifications for such API; and that the manufacturer of the API provides letters of authorization necessary or useful for the FDA to access the DMF for the API to the extent necessary or useful to support Bion's efforts to obtain and maintain Regulatory Approvals for the Product in the Territory. The Parties shall also take steps to identify an alternate source for API no event later than twelve (12) months after the filing of Regulatory Approval for the Product in the Territory.

ARTICLE 5. PRODUCT ORDERS; DELIVERY

5.1 Manufacture and Supply of Product. Subject to the receipt of marketing approval, Bion hereby appoints CoreRx to Manufacture Product at the Facility. CoreRx accepts such appointment to Manufacture Product and to do such other acts as are herein authorized. Subject to the terms and conditions of this Agreement, CoreRx shall Manufacture and supply to Bion, and Bion shall purchase from CoreRx, Product that is ordered by Bion pursuant to Firm Orders submitted in accordance with this Agreement. Product shall be Manufactured and supplied by CoreRx in accordance with this Agreement and the relevant Firm Order. Subject to the terms and conditions of this Agreement, each Firm Order shall be considered a separate Firm Order and shall be valid and binding upon its submission by Bion in accordance with this Agreement. Bion shall purchase the Products exclusively from Core Rx and CoreRx shall Manufacture and supply the Products exclusively for Bion and not for any Third Party. Product Manufactured under this Agreement pursuant to Firm Orders shall be the exclusive property of Bion.

5.2 Monthly Forecast. During the Term of this Agreement, Bion shall provide to CoreRx, on a monthly basis, a non-binding rolling forecast of its Product requirements for the next twelve (12) months (or for the remainder of the Term, whichever is less). The forecasts for the first three (3) months of any 12-month period shall represent binding purchase obligations of Bion with respect to the Products.

5.3 Firm Orders. Bion shall place Firm Orders for its requirements of each Product at least ninety (90) days before the requested Delivery Date unless an alternative lead time for a given Product is otherwise agreed, in which event Bion shall place such Firm Order no later than the number of days equal to such lead time. Firm Orders will be made on such form of purchase order or document as Bion may specify from time to time in writing; provided that the terms and conditions of this Agreement shall be controlling over any terms and conditions included in any Firm Order. Any term or condition of such Firm Order that is different from or contrary to the terms and conditions of this Agreement shall be void, unless otherwise agreed between the Parties in writing.

5.4 Delivery Against Firm Orders. CoreRx will acknowledge all Firm Orders within five (5) days following receipt of same and will deliver all orders within ninety (90) days following the date such Firm Order is received. CoreRx will accept all Firm Orders for a particular calendar month to the extent that the Firm Order (a) does not exceed the amount of the binding Forecast for such calendar month by more than twenty percent (20%), and (b) requires delivery no less than ninety (90) days following the date on which CoreRx receives the Firm Order. CoreRx will not be in breach of this Section 5.4 if CoreRx's failure to supply Products is due to a Force Majeure event or if CoreRx's failure is limited to quantities in excess of the quantities specified in this Section 5.4; provided that CoreRx shall use Commercially Reasonable Efforts to Manufacture additional quantities of Product that exceed 120% of the binding forecast. CoreRx shall Deliver Product under each Firm Order no later than the Delivery Date specified in the applicable Firm Order; provided, however, that no Delivery of Product shall be

made more than two (2) Business Days in advance of the date specified for Delivery in a Firm Order without Bion's prior written approval. The Facility shall be indicated on documents accompanying each shipment of Product. In the event CoreRx will fail to meet a Delivery Date set forth in a Firm Order, CoreRx shall bear the incremental costs required for expedited transport above and beyond the cost incurred by the method outlined in the Delivery Terms.

5.5 Cancellation or Deferral. Bion may cancel or defer any Firm Order, in whole or in part, without penalty, provided that such cancellation or deferral notice is received by CoreRx 15 days prior to CoreRx's scheduled commencement of the manufacture of the Product under such Firm Order. If Bion cancels or defers a Firm Order, in whole or in part, with less than the aforementioned notice, CoreRx shall use its best efforts to minimize any charges to Bion

5.6 Delivery. CoreRx shall effect Delivery of each Firm Order in accordance with the Bion Intellectual Property, Applicable Laws (including cGMPs) and the Product Specifications (and for clarity, CoreRx shall only effect Delivery of Product pursuant to a Firm Order). CoreRx shall Deliver or arrange for Delivery of Product to the Delivery Address and in accordance with the Delivery Terms, in order to fill such Firm Order. Each container shall be marked as to the identity of the Product, the quantity of Product, the related Firm Order number, the related Bion product code and any other information required by the Firm Order. CoreRx shall bear all risk of loss or damage with respect to Product(s) until such Product(s) are Delivered to Bion. Each Delivery of Product shall be accompanied by a packing slip and a Material Safety Data Sheet for such Product. CoreRx shall also provide Bion with Agency certification, for those countries in which the applicable Agency is in the practice of requiring any such certifications.

5.7 Transfer of Title. Title to Product supplied hereunder shall pass to Bion contemporaneously with the transfer of risk of loss, as established by the Delivery Terms.

5.8 Packaging. All Product supplied hereunder shall be packaged in accordance with the Quality Agreement, and CoreRx shall ensure that such packaging is otherwise in accordance with the Bion Intellectual Property and Applicable Laws (including cGMPs), as well as the applicable Product Specifications. Without limiting the foregoing, all Product supplied hereunder shall also be labeled with a traceable batch number and the date of Manufacture. In addition, the packing slip shall contain gross, tare and net weights of the Product.

5.9 Handling and Storage Prior to Delivery. Prior to Delivery of Product to Bion, CoreRx shall handle and store all Product (including all Materials used in the Manufacture of such Product) in accordance with the Bion Intellectual Property and Applicable Laws (including cGMPs), as well as the applicable Product Specifications.

5.10 Certificate of Analysis. Prior to Delivery of Product CoreRx shall provide to Bion a certificate of analysis (COA) and a Certificate of Compliance (COC) for all manufacturing Batches. The COA shall contain the following information: (i) name, address, and contact phone number of the Facility where the Product was Manufactured, (ii) Product name, (iii) CoreRx batch number, (iv) date of Manufacture, (v) date of release, (vi) date of expiry, (vii) a list of each test performed, the acceptance limits as indicated in the Product Specifications, and the results obtained (and the COA should document actual values, where specifications are quantitative, and maintain the significant figures and rounding of numbers defined in the Product Specifications); and (vii) a release statement signed and dated by CoreRx indicating that the batch: (1) meets the Product Specifications; (2) was Manufactured in accordance with cGMPs, ANDAs, Applicable Laws, DMF (if applicable), the Bion Intellectual Property, and the controlled validated process; and (3) used only Materials that met their specifications. The COA should clearly state if reduced or skip lot testing is used to release the lot of Product provided to Bion. The CoreRx shall list only those process changes that required Bion review and approval in accordance with the Quality Agreement, manufacturing deviations (as defined in the Quality Agreement) and out of Product Specification (OOS) investigations applicable to the Product. In addition, a Certificate of Compliance shall be provided to Bion, which document shall be used to notify

Bion of any process changes, rework, reprocessing, significant manufacturing deviations, or OOS investigations associated with the Batch. CoreRx shall not Deliver Product unless and until such Product has been quality released by Bion based upon such COA. If quality control release of the Product is delayed for more than ninety (90) days due to an investigation, CoreRx will provide all necessary assistance to close any deviation in less than thirty (30) days thereafter.

5.11 Supply Interruption. If CoreRx is unable to supply any Product ordered by Bion in accordance with the terms of this Agreement, then CoreRx shall use Commercially Reasonable Efforts to remedy the problem or secure an alternative source of supply within a reasonable time at no cost to Bion, and any such alternative source of supply shall be on terms substantially identical with the terms of this Agreement. If CoreRx is unable to remedy the problem or secure an alternative source of supply within two (2) months after its initial failure to supply, then CoreRx shall consult with Bion and the parties shall work together to remedy the problem. If CoreRx is unable to remedy the supply problem after an aggregate period of three (3) months (or longer as agreed in writing by the Parties), commencing with the date upon which such failure to supply began, then Bion shall have the right (but not the obligation), to take the following actions with respect to the affected Product:

(i) Bion may cancel any outstanding Firm Order for such Product, and Bion shall have no obligation to CoreRx for any Firm Order of the Product to the extent the Product has not been supplied as of the date of delivery of such cancelation notice; and/or

(ii) if CoreRx is unable to the Product for a period exceeding one hundred and twenty (120) days from the confirmed delivery date on two consecutive occasions during any twelve (12) month period (**"Supply Interruption"**) then Bion may have the applicable Product manufactured by an Approved Manufacturer rather than by CoreRx. With respect to any Supply Interruption, CoreRx shall reimburse Bion within thirty (30) days of written demand for any actual cover costs paid by Bion to any customer of Bion or its Affiliates pursuant to Bion's ordinary course contractual arrangement with such customer providing for payment to such customer in the event of a failure of supply of any Product by Bion or its Affiliates ("**Cover Costs**"), provided that Bion shall use Commercially Reasonable Efforts to mitigate such Cover Costs including by using any available safety stock and canceling orders promptly upon notice of a Supply Interruption.

5.12 Business Failure. If, from time to time during the Term, a Business Failure occurs, then Bion shall have the right (but not the obligation) to exercise the rights and remedies set forth in Section 5.12, and in connection therewith, the provisions set forth in Section 5.12 shall apply, mutatis mutandis.

5.13 Subcontracting. Prior to engaging a given Affiliate or Third Party subcontractor to perform any Manufacturing activities hereunder, CoreRx shall notify Bion thereof and discuss such subcontracting with Bion; provided that in all cases, CoreRx shall not subcontract any of its obligations hereunder, including any obligations to Manufacture any Product, to an Affiliate or Third Party without the prior written consent of Bion. With respect to any subcontracting (including to an Affiliate or a Third Party), CoreRx shall remain fully responsible and liable for all obligations hereunder, and fully guarantees and warrants the performance (in accordance with this Agreement) of any responsibilities so subcontracted, and assumes full vicarious liability for such activities performed by any subcontractor. Without limiting the foregoing, CoreRx shall cause any and all such subcontractors to comply with the applicable terms and conditions of this Agreement (including with respect to technology transfers (including as set forth in Section 5.14), intellectual property ownership provisions (including as set forth in Article 11) and any and all audit and inspection rights, including under Article 9). Any subcontracting of any Manufacturing or other activities hereunder shall be subject to the other applicable terms and conditions of this Agreement, in each case, to the extent applicable. Notwithstanding the foregoing, the use of a Third Party subcontractor shall not result in any increase in the Transfer Price, unless Bion expressly agrees in writing to an increase in the Transfer Price as a result thereof.

5.14 Approved Manufacturer. CoreRx shall, within thirty (30) days of Bion's request at any time after a Product has received Regulatory Approval, assist Bion in the designation, qualification and

maintenance of Bion or its' designee as an alternative supplier of such Product (each, an "**Approved Manufacturer**") in the event of a Supply Interruption. Bion shall require any Approved Manufacturer to agree in writing to observe the terms of this Agreement relating to confidentiality and the manufacture of Products. CoreRx will (i) provide the Approved Manufacturer copies of the physical embodiment of all processes, protocols, procedures, methods, tests and other know-how, relating to the Manufacturing of such Product and (ii) make available to the Approved Manufacturer via telephone or email, on a mutually convenient timetable, reasonable technical assistance with respect to the Manufacture of Product(s). In addition, upon the request of Bion from time-to-time during the Term, CoreRx shall provide reasonable technical assistance to the Approved Manufacturer with respect to such Approved Manufacturer's receipt, adoption and establishment of the manufacturing process for the Product, including: (a) allowing representatives of Approved Manufacturer to observe the manufacturing process at the Facilities, on a mutually convenient timetable, in connection with such transfer, (b) supplying analytical test methods and other testing know-how including method validation reasonably required to perform release testing or other testing as may be required by the applicable Agency or other regulatory authority, and (c) providing Approved Manufacturer with appropriate quantities of reference standards and samples related to such Product in order to facilitate its testing. In addition, (i) Approved Manufacturer shall have the right to reference CoreRx's (and its Affiliates') regulatory filings and such other regulatory submissions controlled by CoreRx (or any its Affiliates) reasonably necessary for the manufacture of such Product, and CoreRx (and its Affiliates) shall grant, and hereby does grant, to Approved Manufacturer such right of reference and (ii) Approved Manufacturer shall have the right to use any know-how owned or otherwise controlled by CoreRx or any of its Affiliates to make, have made and use the Products.

5.15 Samples. Upon Bion's request, CoreRx will provide to Bion, at no additional cost, samples of Product from a Bion-specified Batch in quantities reasonably requested by Bion for inspection, testing and analysis. CoreRx will ship such samples as requested by Bion to a Bion designated address.

5.16 Assistance with Regulatory Filings. CoreRx shall be responsible for preparing documents to support ANDAs or other filing submissions for Products, as reasonably required by Bion, and shall provide a copy of such documents to Bion for review prior to submission to Agency by Bion. CoreRx shall continue to provide all such documents reasonably requested by Bion for maintenance of such ANDAs or other filing submissions. CoreRx shall continue to provide ongoing support reasonably requested by Bion for ANDA for each of the Products. CoreRx shall be responsible, at its cost, for receiving and maintaining any Facility licenses, authorizations, accreditations, permits and/or registrations granted or filed with an Agency, including those required for Manufacture of Products. CoreRx shall also provide Bion with Agency certification, for those countries in which the applicable Agency is in the practice of requiring any such certifications. For clarity, Bion shall be permitted to share information provided by CoreRx under this Section 5.16 with Affiliates and Third Parties (including sublicensees and Agencies) and such Affiliates and Third Parties shall be entitled to use such information in support for Products. If any Products are to be filed by Bion, in its sole discretion, in another country, and Bion selects to work with CoreRx in these countries, CoreRx will provide the support and cooperation for filing and work with Bion to get the Facility inspected and approved by the applicable country Agency, subject to mutually acceptable economic terms to be reached by the Parties.

5.17 Product Supply. CoreRx shall Manufacture and supply Products exclusively for Bion and not for any Third Party.

5.18 Exclusivity. Except as pursuant to this Agreement, neither Party nor their respective Affiliates shall for the duration of the Term of this Agreement develop or manufacture (including contract manufacturing) any other Drug Product for sale or distribution in the Territory that references the ANDA for the Reference Product or any foreign equivalent outside the Territory (regardless of whether such Product(s) are marketed under a generic, branded or private label) to any Third Party if either Party knows or has reason to know that such product will be sold or distributed in the Territory during the Term of this Agreement in the Territory. In providing or granting any rights to the Product outside the

Territory, the Parties shall obtain from each such grantee, licensee, beneficiary or acquiree (including Affiliates) of such rights their binding written agreement that they shall only sell and distribute the Product(s) within their specified territory, and not within any part of the Territory during the Term of this Agreement.

ARTICLE 6. FINANCIAL PROVISIONS

6.1 Except as explicitly provided in this Agreement, each Party shall be solely responsible for all costs and expenses associated with carrying out its responsibilities under this Agreement. The Product shall be manufactured at CoreRx's manufacturing facility that is FDA inspected and approved, and meeting all FDA requirements for manufacturing, pilot batches (engineering batches), exhibit (submission) batches, conduct stability studies and produce stability reports in form and substance capable of supporting FDA approval of the ANDA for the Product. For the sake of clarity, all costs for any external, out-of-pocket development costs including but not limited to: finished Product formulation development, finished Product analytical method transfer, project management, equipment qualification, engineering batch and registration batch engineering, pilot, pivotal or exhibit batches (excluding API required for such development batches) hereafter shall be borne by CoreRx.

6.2 Transfer Price. For each unit of Product ordered by Bion under Firm Orders hereunder and supplied by CoreRx to Bion in accordance with the terms and conditions of this Agreement, Bion shall pay CoreRx the Transfer Price, which payments shall be made in accordance with Section 6.8. The Transfer Price shall be established by mutual agreement of the Parties on an annual basis one (1) month prior to the commencement of Bion's next fiscal year, and once established shall remain in effect for the applicable fiscal year. When establishing the Transfer price for any fiscal year, the Parties shall each seek to identify opportunities to negotiate more favorable Materials prices. Notwithstanding the foregoing, the Transfer Price may be increased during a fiscal year if the cost of a Material increases by 10% of the cost for that Material upon which the most recent Transfer Price was based

6.3 Productivity/Cost Improvements. CoreRx agrees to use Commercially Reasonable Efforts to identify and implement all potential areas of cost improvement. At the request of Bion, appropriate representatives of Bion and CoreRx shall meet from time to time during the Term to discuss and agree on (a) objectives for a continuous improvement program, including cost improvements ("**Continuous Improvement Program**") and (b) the means of measuring and implementing the results of the Continuous Improvement Program. Progress against objectives shall be measured quarterly. CoreRx shall use all reasonable endeavors to achieve the agreed objectives and targets identified for the relevant period. The net benefits of cost reductions and improved efficiencies shall be shared equally by the Parties, including as reductions to the Transfer Price under this Agreement. In such case, the Parties shall reasonably discuss and agree on the amount of such reductions to the Transfer Price.

6.4 Records. Each Party shall keep and maintain or cause to be maintained books and records pertaining to its activities in connection with this Agreement.

6.5 Reserved.

6.6 **Invoicing, Payment and Taxes.** (a) Upon shipment of a Product to Bion, CoreRx shall submit invoices therefor to Bion. Bion shall pay each invoice within sixty (60) days from the date the Product arrives at Bion's designated port. All payments under this Agreement shall be made in U.S. Dollars.

(b) CoreRx shall be liable for all income and other taxes (including interest) ("**Taxes**") imposed upon any payments made by Bion to CoreRx under this Agreement.

ARTICLE 7. QUALITY

7.1 Compliance and Investigation. CoreRx shall Manufacture and supply Product in accordance with the Quality Agreement, the Product Specifications and Applicable Laws (including cGMPs) and strictly in accordance with the Bion Intellectual Property and any applicable DMF. CoreRx shall notify Bion immediately of any difficulty in Manufacturing Product in accordance with all of the terms and conditions of this Agreement. Bion may, at its option, investigate the cause of any failure, or require CoreRx to do so and provide Bion with a written report summarizing the results of CoreRx's investigation. CoreRx shall complete any quality investigation within the number of days established in the Quality Agreement.

7.2 Audits and Inspection of Facility. From time to time as requested by Bion, CoreRx shall permit one or more qualified technical specialists from Bion (or its designee), upon reasonable prior notice and during normal business hours, to conduct audits (including quality, safety and environmental) and other inspections of the Facility or any other facility which is proposed to be used to Manufacture Product, provided such audits shall not last more than five (5) days per site (or such longer period of time as Bion (or its designee) may reasonably require to conduct such audit or inspection). Bion shall not be obligated to pay CoreRx for such visits, but Bion shall be solely responsible for its out-of-pocket costs to conduct such site visits. Observations and conclusions of Bion's audits and inspections will be issued to CoreRx. CoreRx shall provide a written response within fifteen (15) Business Days of receipt of such observations and conclusions. The Parties will discuss such response and promptly agree on corrective action to be implemented. The agreed corrective action shall be implemented by CoreRx, at CoreRx's expense. If reasonably necessary (as determined by Bion), Bion shall have the right, at CoreRx's expense, to direct any actions with respect to implementation of corrective action with the assistance of CoreRx in order to ensure that any such corrective actions are appropriately completed. Bion may, in its sole discretion, suspend any Firm Orders until the agreed corrective action has been fully implemented. Bion shall have the right to review all relevant documentation.

7.3 Quality Control Tests. CoreRx shall perform, at its quality control laboratories, such quality control tests as are indicated in the Bion Intellectual Property and the Product Specifications, in accordance with the test methods and procedures described by Bion. The final release of each Batch of Product shall be done by Bion following the process specified in the Quality Agreement, and the procedures to be followed in the event of a Batch failure are specified in the Quality Agreement. Core Rx shall be responsible for any Batch failure unless the failure is not associated with any testing Manufacturing or packaging process carried out by CoreRx as provided in this Agreement.

7.4 Production Batch Failure. Should any production Batch fail to meet the quality control Specifications, or be produced in a manner not corresponding to the Bion Intellectual Property or Bion-approved Manufacturing documents or not in accordance with Applicable Laws (including cGMPs), CoreRx shall immediately notify Bion. Such Batch shall not be Delivered hereunder.

7.5 Retention Samples. CoreRx is responsible for maintaining, retaining and storing retention samples sufficient to perform full specification analyses, which storing and testing are as indicated in the Bion Intellectual Property and/or the Specifications, as applicable. Such amounts shall be retained for the longer of (i) the expiration period of the Product plus one (1) year or (ii) such longer period of time as may be required by the Applicable Law.

7.6 Notification of Agency Action. Each Party shall immediately notify the other Party of any information such Party receives regarding any threatened or pending action by any Agency that has the potential to impact any Product supplied to Bion hereunder, including any Agency non-approval or regulatory action. Upon receipt of any such information, the Parties shall consult in an effort to arrive

at a mutually acceptable procedure for taking appropriate action; provided, however, that nothing contained herein shall be construed as restricting the right of either Party to make a timely report of such matter to any Agency or take other action that it deems to be appropriate or required by Applicable Law.

7.7 Safety or Efficacy Claims. Each Party shall immediately notify the other Party of any information of which it is aware concerning Product supplied to Bion which may affect the safety or efficacy claims or the continued marketing of the Product. Any such notification will include all related information in detail. Upon receipt of any such information, the Parties shall consult in an effort to arrive at a mutually acceptable procedure for taking appropriate action; provided, however, that nothing contained herein shall be construed as restricting the right of either Party to make a timely report of such matter to any Agency or take other action that it deems to be appropriate or required by Applicable Law. Each Party will notify the other immediately of any health hazards with respect to Product which may impact employees involved in the Manufacturing of Product.

7.8 Complaints. Each Party shall immediately notify the other Party of any complaints received by such Party concerning a Product supplied hereunder. CoreRx shall investigate complaints as requested by Bion and shall take corrective action to avoid future occurrences.

7.9 Agency Inspection. CoreRx hereby agrees to notify Bion in writing immediately of any proposed visit or inspection by any governmental authority, including, any Agency (such as the FDA, DEA, etc.) or any environmental regulatory authority if such visit or inspection has the potential to impact Product, and agrees to permit one qualified representative of Bion to be present on site if requested by Bion. CoreRx hereby agrees to advise Bion, without undue delay, after the commencement of any unannounced visit or inspection relating to the Facility or the Manufacture of Products by any governmental authority (even if such visit constitutes a pre-approval inspection or similar review), including any Agency or any environmental regulatory authority, and agrees to permit one or more qualified representative(s) of Bion to be present on site for the portion of the audit affecting Product if requested by Bion. If Bion is not present during such proposed or unannounced visit or inspection, CoreRx shall provide brief daily summary reports during the course of the inspection to the extent the inspection relates to the Manufacture of Products. CoreRx shall promptlyprovide a written summary report of the results of the inspection to Bion in English to the extent the inspection relates to the Manufacture of Products. CoreRx shall promptly (and in no event later than one (1) Business Day) furnish Bion summaries of all observations, notes, reports, documents or correspondence with respect to any Agency requests or inspections of the Facility related to the Manufacture of Products, as well as a copy of each such observation, notes, report, document or correspondence and any proposed corrective actions, responses and other changes arising out of such review or inspection by such Agency. To the extent any of the Agency observations or requests relate to the Facility or the Manufacture of Products, CoreRx shall fully cooperate with Bion and take into consideration any of Bion's inputs, suggestions and other corrective measures to address any of such Agency's concerns and permit one or more qualified representative(s) of Bion to observe and assist CoreRx in responding to such Agency's observations. CoreRx shall fully apprise Bion of any corrective measures effectuated as a result of any inspection and permit one or more qualified representative(s) of Bion to ensure such corrective measures have adequately been implemented in accordance with the timelines and criteria and other commitments made by CoreRx to the Agency in question.

7.10 Restricted Categories. CoreRx hereby declares and covenants that as of the Effective Date of this Agreement it is not, and during the Term shall not, produce, package, label, warehouse, quality control test (including in-process, release and stability testing), release or ship any chemical entity classified as penicillin's, hormones, alkaloids, Beta-lactam antibiotics such as cephalosporin's, carbapenems or monbactams; sex hormones, cytotoxic or cytostatic anti-neoplastic agents; other highly active compounds; biological preparation containing live viruses or microorganisms; or other toxic,

non-drug substances or live agents "technical poisons" including pesticides, herbicides, fungicides, in the Facility.

7.11 Labeling. Bion may specify required labeling on Product and all components and containers. CoreRx will comply with all specified labeling as to each Product and each component and container and shall use only labeling which has been approved in writing by Bion in advance. CoreRx shall not use Bion labels on any products except Product for which such use has been approved by Bion. CoreRx shall not modify the Bion labels in any way without Bion's prior written consent.

7.12 Materials. CoreRx shall maintain an adequate system, which functions as a risk-based assessment of its suppliers of Materials that are components of or may come in contact with the Product (such as primary packaging materials, excipients, and APIs). Furthermore, Bion may, at its option, independently conduct audits or participate in CoreRx audits (including quality, safety and environmental) of CoreRx's suppliers of such Materials, on a routine or for-cause basis. As a result of such audits, if necessary, Bion shall have the right to direct CoreRx to disqualify a supplier as a source of Materials. CoreRx shall identify a new supplier as a source of Materials and replace the disqualified supplier with such new supplier, pursuant to the provisions set forth in Section 3.6. Notwithstanding the foregoing, CoreRx shall be fully responsible for sourcing and testing of Materials, qualification and management of its supplier(s) of Materials.

7.13 Batch Records. CoreRx shall provide Bion with all Batch records and any investigation or deviation reports related to Product for each Batch. Investigations into process deviations must be approved by Bion.

7.14 Data Sets. CoreRx will on an ongoing basis collect, graph, trend, and analyze data of and from the Manufacturing of each Batch of Product, and the accumulated data from all Batches of Product shall be the data set (**"Data Set"**). CoreRx will update the Data Set promptly following the Manufacture of each Batch of Product. The Data Set will include the following Manufacturing data for each Batch of Product, as may be modified by Bion from time to time: yield; cycle-time; lot numbers of Materials used; in-process testing results; Critical Process Parameters (or CPPs); Critical Quality Attributes (or CQAs); and Proactive Process Analysis (PPA). On or before the last day of each calendar month during the Term, CoreRx will update the Data Set (in graphical format, as appropriate) in writing to include each Batch of Product Manufactured during the month; complete review and approval of the Data Set by CoreRx management; and submit the approved Data Set in writing to Bion for review. The Parties acknowledge the Data Set will, among other things, provide the basis for ongoing process improvement and trend analysis. In the event that a deviation occurs during the Manufacturing of a Batch of Product, as part of the investigation of such deviation pursuant to Section 12.3, CoreRx will update the Data Set to include the data for such Batch within seven (7) calendar days of the occurrence or identification of such deviation, whichever is later; and CoreRx will generate run charts of data (from the updated Data Set) which include data from not less than ten (10) consecutive batches of Product Manufactured immediately preceding the deviation event to establish a baseline of Manufacturing performance against which the deviation Batch data may be compared. CoreRx shall be responsible for ensuring, verifying and delivering this Data Set.

7.15 Quality Agreement. The Parties shall negotiate in good faith and enter into a Quality Agreement with respect to the Manufacture of such Product within a reasonable time prior to the anticipated First Commercial Sale of the first Product. The Parties shall also negotiate in good faith and enter into a Safety date Exchange Agreement covering safety data exchange, adverse event reporting, patient support and management of patient compliance concerning the Products.

ARTICLE 8. REGULATORY MATTERS

8.1 Records. CoreRx shall retain all records related to the (i) Manufacture of Product(s) for a period of not less than two (2) years from the expiration of the approved shelf life of the Product(s) to which said records pertain (or such longer period as required by Applicable Law) and (ii) Manufacture of Validation batches for five (5) years past the effective date of termination of this Agreement or two (2) years beyond the approved shelf life of the applicable Product(s), whichever is shorter (or such longer period as required by Applicable Law) (each such period shall be referred to as the "**Retention Period**"). CoreRx shall provide Bion with complete and accurate copies of the appropriate documents for each production Batch, upon Bion's request. CoreRx shall, at the end of the Retention Period, either destroy the records or return the records to Bion at Bion's written instructions.

8.2 Audit Rights. CoreRx's Records shall be open to inspection and subject to audit and/or reproduction, during normal working hours, by Bion or its authorized representative (i) as required by governmental authorities or (ii) as may desirable by Bion for any other valid business purpose. CoreRx shall preserve such Records for a period of ten (10) years after the end of the Term or for such longer period as may be required by Applicable Law. For the purpose of such audits, inspections, examinations and evaluations, Bion or its authorized representative shall have access to such records beginning on the Effective Date and continuing until ten (10) years after the satisfaction of CoreRx's obligations under this Agreement. In addition, CoreRx shall provide adequate and appropriate workspace for Bion or its authorized representatives to conduct such audit. Bion or its authorized representative shall give CoreRx reasonable advance notice of an intent to audit.

8.3 Subcontractors. For clarity, CoreRx shall ensure that any subcontractor performing any Manufacturing activities complies with the foregoing provisions of Sections 8.1 and 8.2.

8.4 Decisions on Recalls. As between the Parties, Bion shall have the sole and absolute discretion as to whether to institute a recall or withdrawal Product (whether instituted at the request of an Agency or voluntarily instituted by Bion for any reason); provided that, to the extent practical, Bion shall notify CoreRx thereof prior to implementation. Notwithstanding anything to the contrary contained herein, CoreRx shall have no right to institute any recall or withdrawal of any Product. CoreRx agrees to abide by all decisions of Bion to recall or withdraw Product.

8.5 Recalls. In the event that Product(s) are recalled or withdrawn, CoreRx shall fully cooperate with Bion in connection with such recall or withdrawal. If such recall or withdrawal is caused by Product that contains a Deficiency or by CoreRx's negligence or breach of this Agreement, CoreRx shall reimburse Bion for (i) all costs associated with the manufacturing of the recalled or withdrawn Product, including the Transfer Price for Product and other formulation, packaging and distribution expenses o Product (and including materials used in connection therewith), and (ii) all expenses incurred in connection with such recall or withdrawal.

8.6 Marketing Authorizations. As between the Parties, Bion (or its designee) shall have the sole right to prepare and file ANDAs for the Products with the applicable governmental authorities. Without limiting CoreRx's obligations under Section 5.16, CoreRx shall provide Bion with such information and assistance as Bion may reasonably request for purposes of applying for and maintaining any ANDAs for Product including providing Bion with all reports, authorizations, certificates, methodologies, specifications and other documentation in the possession or under the control of CoreRx (or any of its Affiliates) relating to the Manufacture of Product or any component thereof for such filings.

8.7 DMFs. Without limiting CoreRx's obligations under Section 5.16, CoreRx shall provide Bion with such information and assistance as Bion may reasonably request for purposes of applying for and maintaining any DMFs, as applicable, for Product Manufactured and supplied under this Agreement.

8.8 Disclosure of Audits. CoreRx acknowledges that governmental authorities (including Agencies) may, in conducting an inspection of Bion, request copies of reports of Bion audits of its suppliers. For clarity, in response to such a request, Bion may provide to the governmental authority (including any Agency) the report of any compliance audit conducted in accordance with this Agreement or the Quality Agreement.

ARTICLE 9. COMMERCIALIZATION

9.1 Marketing, Sales and Distribution Obligations. Bion shall be responsible for all decisions regarding Commercialization of the Product or Products.

9.2 Commercialization Outside the Territory. For the avoidance of doubt, it is understood and agreed that Bion, as the holder of the ANDA for each Product shall have the right to commercialize any Product that has received final Regulatory Approval for sale in the Territory in countries that are outside the Territory, provided that If Bion requests that CoreRx provide a technology transfer for the production of the applicable Product outside the Territory for Commercialization outside the Territory, then CoreRx shall receive a technology transfer payment from the new manufacturer or the entity marketing the Product in the new countries.

ARTICLE 10. INTELLECTUAL PROPERTY

10.1 Bion Intellectual Property. As between the Parties, Bion shall own all right, title and interest in and to the Bion Intellectual Property (including any and all information and data contained therein), and CoreRx is not acquiring any ownership interest in any Bion Intellectual Property (including any and all information and data contained therein) hereunder.

10.2 CoreRx Intellectual Property. As between the Parties, CoreRx shall own all right, title and interest in and to the CoreRx Intellectual Property, and Bion is not acquiring any ownership interest in any CoreRx Intellectual Property hereunder. CoreRx agrees and acknowledges that no information, know-how, data or other intellectual property, other than the Bion Intellectual Property, shall be used by or on behalf of CoreRx in the Manufacture of Products hereunder. If CoreRx uses any CoreRx Intellectual Property in the Manufacture of any Product then Bion shall have a non-exclusive, perpetual, irrevocable, paid-up and royalty-free license, including the right to grant sublicenses, under such CoreRx Intellectual Property to the extent necessary or useful for Bion to Develop, Manufacture or Commercialize the applicable Product.

10.3 Grant of License. Bion hereby grants to CoreRx a non-exclusive license to use, the Bion Intellectual Property solely to Develop the Products in accordance with this Agreement and to Manufacture Products for Bion in accordance with this Agreement. Unless otherwise consented to by Bion in writing, (i) CoreRx shall not use the Bion Intellectual Property (or any Specifications or any DMF) for any purpose other than the the Manufacture of Products for Bion hereunder and (ii) CoreRx shall not use any proprietary and/or confidential information or data of or provided by Bion or its Affiliates in the Manufacture of Product hereunder other than the Bion Intellectual Property.

10.4 Improvements. (a) Unless otherwise agreed in writing, all discoveries, improvements and/or inventions by CoreRx or any of its Affiliates, whether patentable or not, resulting from CoreRx's or its Affiliates' use of the Bion Intellectual Property or the Manufacture of Products shall be the sole and exclusive property of Bion ("**Bion Improvements**"), and shall be deemed to be Bion Confidential Information. For the avoidance of doubt, Bion Improvements shall automatically become part of Bion Intellectual Property and shall be subject to the license referenced in Section 10.3.

(b) Each Party shall promptly notify the other Party if it becomes aware of any Bion Improvement, and CoreRx shall reasonably assist Bion in protecting Bion's proprietary rights any Bion Improvement. CoreRx hereby represents and warrants to the Bion that all of its employees, officers, independent contractors, and agents who may perform activities under this Agreement have executed agreements (prior to performing any activities under this Agreement) requiring assignment to CoreRx of all

intellectual property made in performing activities under pursuant to this Agreement. CoreRx shall (at Bion's reasonable expense) take all reasonable additional actions and execute such agreements, instruments, and documents as may be reasonably required to perfect Bion's right, title, and interest in, to, and under Bion Improvements.

10.5 IP Enforcement Matters. If either Party learns of any actual or threatened infringement or misappropriation or any attack on the validity or enforceability by a Third Party with respect to Bion Intellectual Property anywhere in the Territory, such Party shall promptly notify the other Party and shall provide such other Party with available evidence of such events. Bion shall have the first option to pursue any enforcement or defense of Bion Intellectual Property against infringement or misappropriation, including defense against a declaratory judgment action alleging invalidity or non-infringement of any of the Bion Intellectual Property; provided, that Bion pays all costs and expenses related to the same, keeps CoreRx reasonably informed of its progress and provides CoreRx with copies of any substantive documents related to such proceedings and reasonable notice of all such proceedings. Any recovery of damages or other sums recovered in a proceeding or action covered by this Section 10.5 shall be applied first in satisfaction of any unreimbursed expenses and legal fees of Bion and next, if applicable, in satisfaction of the costs and expenses incurred by CoreRx in connection therewith, including reasonable attorneys' fees involved in the prosecution and/or defense of any proceeding or action and, if after such reimbursement any funds shall remain from such damages or other sums recovered, the remaining recovery shall be retained one hundred percent (100%) by Bion. In any infringement or misappropriation suit that Bion may institute to enforce Bion Intellectual Property, or in any declaratory judgment action alleging invalidity, non-infringement or non- misappropriation of any Bion Intellectual Property brought against CoreRx or Bion, the other Party shall, at the request and expense of the Party initiating or defending the suit or action, cooperate and assist in all reasonable respects, having its employees testify when requested and making available relevant records, papers, information, specimens and the like. In addition, upon the reasonable request of the Party instituting an action under this Section 10.5, or if required by Applicable Law, the other Party shall join such action and shall be represented using counsel of its own choice, at the requesting Party's expense; provided, that if Bion does not initiate an action hereunder on the advice of outside patent counsel, then CoreRx may not require Bion to join such action but CoreRx may have Bion join such action as an involuntary Party, but Bion shall not be required to participate in such action.

10.6 **IP Defense Matters**. If any notice of infringement or misappropriation is received by, or a suit is initiated against, Bion or CoreRx by a Third Party concerning the Manufacture, use, importation, offer for sale, or sale of a Product in the Territory, the Parties shall consult in good faith regarding the best response before either Party responds to the Third Party.

ARTICLE 11. CONFIDENTIALITY AND PUBLIC DISCLOSURE

11.1 Confidential Information. (a) During the Term of this Agreement and for five (5) years thereafter without regard to the means of termination, each Party (i) shall maintain in confidence all Confidential Information of the other Party; (ii) shall not use such Confidential Information for any purpose except as permitted by this Agreement; and (iii) shall not disclose such Confidential Information to anyone other than those of its Affiliates, sublicensees, prospective sublicensees, employees, consultants, agents or subcontractors who are bound by written obligations of nondisclosure and non-use no less stringent than those set forth in this Article 11 and to whom such disclosure is necessary in connection with such Party's activities as contemplated in this Agreement. Each Party shall ensure that such Party's Affiliates, sublicensees, prospective sublicensees, employees, consultants, agents and subcontractors comply with these obligations. Each Party shall notify the other promptly on discovery of any unauthorized use or disclosure of the other's Confidential Information.

(b) Notwithstanding the provisions of Section 11.1(a), a receiving Party may disclose Confidential Information of the disclosing Party to the extent such disclosure is (i) made in response to a valid order

or subpoena of a court of competent jurisdiction or other governmental body of a country or any political subdivision thereof of competent jurisdiction; provided, that receiving Party provides the other Party with prior written notice of such disclosure (if practicable) in order to permit the other Party to seek a protective order or other confidential treatment of such Confidential Information; and provided further that any Confidential Information so disclosed will be limited to that information that is legally required to be disclosed in such response to such court or governmental order or subpoena; (ii) otherwise required by Applicable Laws; provided, that receiving Party provides the disclosing Party with prior written notice of such disclosure (if practicable) in order to permit the disclosing Party to seek a protective order or confidential treatment of such Confidential Information; and provided further that any Confidential Information so disclosed will be limited to that information that is legally required by Applicable Law to be disclosed; (iii) made by the receiving Party to a Regulatory Authority, as required to obtain or maintain Regulatory Approvals; provided that reasonable efforts shall be used to ensure confidential treatment of such Confidential Information; (iv) made by the receiving Party to a Third Party as may be necessary or useful in connection with the Commercialization of a Product (including the manufacture of a Product); provided the Third Party is bound by written confidentiality obligations no less protective that those set forth in this Agreement; (v) made by receiving Party to a U.S. or foreign tax authority to the extent legally required by Applicable Laws to be disclosed; (vi) made by receiving Party to its representatives or to Third Parties in connection with sublicensing or financing activities of the receiving Party; provided that the Third Party is bound by written confidentiality obligations no less protective that those set forth in this Agreement; (vii) made by receiving Party or any of its representatives in the filing or publication of Patent Rights relating to the Product to the extent such disclosure in the filing or publication of Patent Rights is reasonably necessary for support of the Patent Rights; (viii) made by receiving Party to comply with Applicable Laws related to securities laws disclosure requirements or any disclosure requirements of any applicable stock market or securities exchange; or (ix) made by receiving Party in compliance with Section 11.2.

11.2 Press Releases and Public Announcements. No public announcement or disclosure may be made by either Party with respect to the subject matter of this Agreement without the prior written consent of the other Party; provided, that the provisions of this Section 11.2 will not prohibit (a) any disclosure required by any applicable legal requirement, including any legal requirement or listing standard of any exchange or quotation system on which the disclosing Party's securities are listed or traded or to be listed or traded (in which case the disclosing Party will provide the other Party with the opportunity to review in advance the disclosure and to contest the same, including reasonable opportunity to seek a protective order or to seek confidential treatment of such disclosures under Rule 24b-2 of the Securities Exchange Act of 1934, as amended), (b) any disclosure made in connection with the enforcement of any right or remedy relating to this Agreement, (c) any disclosure made by Bion or CoreRx to their respective employees, collaborators, licensors, licensees, contract research organizations, business partners, investors, potential investors, lenders and potential lenders provided the person receiving the disclosure has undertaken a confidentiality obligation to Bion or CoreRx, as the case may be, substantially similar to the confidentiality obligations the Parties have undertaken to each other under this Agreement, or (d) any disclosure made pursuant to a press release in a form mutually agreed to by the Parties (or any other subsequent disclosure containing substantially similar information).

ARTICLE 12. REPRESENTATIONS AND WARRANTIES

12.1 General Representations and Warranties. Each of Bion and CoreRx represents, warrants, covenants and agrees that, at all times during the Term, (a) it is a corporation duly organized and validly existing and in good standing under the laws of its jurisdiction of organization, (b) it is qualified or licensed to do business and in good standing in every jurisdiction where such qualification or licensing is required, (c) it has the corporate power and authority to execute, deliver and perform its obligations under this Agreement, and the execution, delivery and performance of this Agreement by it has been duly authorized by all necessary corporate action, (d) this Agreement has been duly executed and

delivered by it, and (e) this Agreement constitutes the valid and binding obligations of it, enforceable against it in accordance with its terms except as enforceability may be limited by bankruptcy, insolvency, reorganization, moratorium or other similar laws relating to or affecting creditor's rights generally, or general principles of equity.

12.2 Representations, Warranties and Covenants for Product. CoreRx represents, warrants and covenants that all Product shall, at the time of Delivery, (a) be Manufactured in accordance with, and shall meet, the Product Specifications, (b) be Manufactured in accordance with all Applicable Laws (including cGMPs) in effect on the day of Delivery, (c) be Manufactured in accordance with any applicable DMF, (d) be Manufactured in accordance with the Bion Intellectual Property (unless otherwise agreed by the Parties writing or in accordance with the Quality Agreement), (e) not be adulterated or misbranded within the meaning of the U.S. Federal Food, Drug and Cosmetic Act (the "**Act**"), or any similar Applicable Law of any other jurisdiction, (f) not be an article that may not, under the provisions of the Act, or any similar Applicable Law of any other jurisdiction, be introduced into stream of commerce, and (g) have at least the Minimum Remaining Percentage of its maximum shelf-life, as evidenced by expiry dating, remaining.

12.3 Inspection. Bion (or its agent) shall inspect at Bion's discretion (based minimally on physical inspection, identity test and review of the certificate of analysis provided by CoreRx pursuant to Section 5.10) the Product following Delivery for variances and defects. If Bion claims that a shipment of Product did not, at the time of Delivery, meet the representations, warranties or covenants specified in Section 12.2 or the quality requirements set forth in Article 8 (a "**Deficiency**"), Bion shall notify CoreRx based on the foregoing inspection within **[**ninety (90)**]** days after receipt of such Product at Bion's (or its designee's) site, which notice shall provide the quantities affected, the basis for the claim and other information reasonably necessary for CoreRx to assess the claim. Notwithstanding the foregoing, if Bion claims that the Deficiency is a Latent Defect, Bion shall have the obligation to provide such notification to CoreRx in writing within ninety (90) days after Bion's discovery of such Latent Defect (or within ninety (90) days after Bion is notified in writing by a Third Party of such Latent Defect, if later). If Bion and CoreRx are unable to agree as to whether such Product contains a Deficiency, the Parties shall cooperate to have the Products in dispute analyzed by an independent testing laboratory of recognized repute selected by Bion and approved by CoreRx, which approval shall not be unreasonably withheld. The results of such laboratory testing shall be final and binding on the Parties on the issue of whether such Product contains a Deficiency. Such testing shall be for the determination of financial liability only and shall not determine releasability of Product. If the Products are determined to not contain a Deficiency, then Bion shall bear the cost of the independent laboratory testing and pay the Transfer Price with respect to the Products in accordance with this Agreement. If the Products are determined to contain a Deficiency, then CoreRx shall bear the cost of laboratory testing, and CoreRx shall, at Bion's election, either replace the rejected Products within **[**thirty (30)**]** days of the date of such determination, at no cost to Bion, or refund to Bion the Transfer Price paid for such Products plus any applicable delivery charge.

12.4 Return or Destruction. Any Product that is determined to contain a Deficiency and that is in Bion's possession shall, at Bion's option, either be returned to CoreRx or destroyed in accordance with Applicable Laws, in each case, at CoreRx's expense.

12.5 Manufacturing Process and Validation. CoreRx represents, warrants and covenants to Bion that (i) the Manufacturing process and test methods for Product (including all future process changes or test method changes prepared in connection with the Manufacture of Product) shall be validated prior to the filling of any Firm Orders; provided, however, that Bion may, in its sole discretion, accept Product from CoreRx prior to the completion of such validation and (ii) the Manufacturing process and test methods (and any change in the Manufacturing process or test methods) for Product shall, in each case, comply with the Applicable Laws (including cGMPs), and any such changes thereto shall be made in accordance with Sections 3.5-3.7 (to the extent applicable) and the Process Change Policy as specified in the Quality Agreement.

12.6 Encumbrances. CoreRx represents, warrants and covenants that, save for security interests expressly given in favor of Bion or its Affiliates, it will have good and marketable title, free and clear of any pledge, lien, restriction, claim, charge, security interest and/or other encumbrance, to all Product to be Delivered hereunder, and all Product supplied to Bion shall be free and clear of all pledges, liens, restrictions, claims, charges, security interests and/or other encumbrances at the time of Delivery.

12.7 Employee Matters. CoreRx represents, warrants and covenants that it shall comply with all rules and obligations vis-à-vis employees and self-employed consultants (if any), used in the Manufacture of Product or otherwise at the Facility, and, as set out by the Applicable Laws, collective and individual agreements, including (a) payment of salaries, social security charges, insurances and withholding taxes on the income received by the workers involved in the performance of this Agreement, as well as (b) any other obligations deriving from the employment agreement and/or self- employment agreement, including provisions protection of the personnel, safety and physical integrity, in full compliance with the Applicable Laws and the individual and collective agreements. CoreRx expressly undertakes to perform this Agreement using only personnel duly employed in accordance with the Applicable Laws.

12.8 DISCLAIMER. EXCEPT AS EXPRESSLY SET FORTH IN THIS AGREEMENT, NEITHER PARTY MAKES ANY REPRESENTATIONS OR WARRANTIES, EXPRESS OR IMPLIED, INCLUDING ANY IMPLIED WARRANTIES OF MERCHANTABILITY OR ANY IMPLIED WARRANTIES OF FITNESS FOR A PARTICULAR PURPOSE OR NON-INFRINGEMENT, ALL OF WHICH ARE HEREBY SPECIFICALLY EXCLUDED AND DISCLAIMED.

ARTICLE 13. INDEMNIFICATION

13.1 Bion Indemnification. Bion shall protect, defend, indemnify, and hold harmless CoreRx, its Affiliates and its and their respective officers, directors, employees, and agents, and their respective successors and permitted assigns ("**CoreRx Parties**") from and against any and all Losses from Third Party Claims to the extent occurring, growing out of, incident to, or resulting directly or indirectly from: (a) a claim by a Third Party that the use of the Bion Intellectual Property by CoreRx (as directed by Bion) to Manufacture Product for Bion hereunder infringes the intellectual property rights of such Third Party; or (b) the sale of a Product by Bion but only in the event such Product was Manufactured by CoreRx in strict accordance with the Product Specifications and otherwise in accordance with the terms and conditions of this Agreement; except in each case to the extent CoreRx is obligated to indemnify Bion pursuant to Section 13.2.

13.2 CoreRx Indemnification. CoreRx shall protect, defend, indemnify, and hold harmless Bion, its Affiliates and its and their respective officers, directors, employees, and agents, and their respective successors and permitted assigns ("**Bion Parties**") from and against any and all Losses from Third Party Claims occurring, growing out of, incident to, or resulting directly or indirectly from: (a) the failure of Product provided by CoreRx hereunder to meet the representations, warranties or covenants set forth in Section 12.2 ; (b) a breach by CoreRx of any of its representations, warranties, covenants, agreements or obligations under this Agreement (including any Addenda) or the Quality Agreement; (c) the negligence, recklessness or willful misconduct of CoreRx in Manufacturing Product or in the performance of its other obligations under this Agreement (including any Addenda) or the Quality Agreement; (d) a Manufacturing Infringement Claim; (e) the acts or omissions of CoreRx, its employees, agents or subcontractors in using the CoreRx Equipment in the Manufacturing of Product, or (f) any breach of the obligations undertaken by CoreRx vis-à-vis its personnel and self-employed consultants, including the obligations regarding salary, social security insurances and taxes.

13.3 Indemnification Procedures. The indemnified Party shall give the indemnifying Party CoreRx (a) prompt written notice of any claims made for which the indemnified Party knows or reasonably should know the indemnifying Party may be liable under the foregoing indemnification and (b) the opportunity to defend, negotiate, and settle such claims. Notwithstanding the foregoing, the failure to give such written notice will not affect the indemnification provided hereunder except to the extent the indemnifying Party shall have been actually prejudiced as a result of such failure. The indemnified

Party shall provide the indemnifying Party with all reasonable information in its possession, and all reasonable authority and all assistance, reasonably necessary to enable the indemnifying Party to carry on the defense of such suit; provided, however, that the indemnified Party reserves the right to retain its own counsel at its own expense to defend itself in such suit

13.4 Settlement. The indemnified Party shall not be responsible to or bound by any settlement made by the indemnifying Party without the indemnified Party's prior written consent, and the indemnifying Party shall not agree to or enter into any settlement without the indemnified Party's prior written consent; provided, however, that the indemnifying Party shall not be required to obtain such consent if the settlement involves only the payment of money and will not result in the indemnified Party becoming subject to injunctive or other similar type of relief and provided that such settlement does not require an admission by the indemnified Party and includes an unconditional release of the indemnified Party from all liability on claims that are the subject matter of such proceeding

13.5 Limitation of Liability. Except for breach of confidentiality obligations under Article 12 AND EXCEPT AS OTHERWISE PROVIDED IN SECTIONS 13.1-13.2, WITH RESPECT TO THIRD PARTY CLAIMS, IN NO EVENT SHALL EITHER PARTY OR ITS AFFILIATES OR ITS OR THEIR RESPECTIVE OFFICERS, DIRECTORS, EMPLOYEES OR AGENTS BE LIABLE TO THE OTHER PARTY OR ITS AFFILIATES OR ITS OR THEIR RESPECTIVE OFFICERS, DIRECTORS, EMPLOYEES OR AGENTS FOR ANY PUNITIVE, INDIRECT OR CONSEQUENTIAL DAMAGES OR INDIRECT OR CONSEQUENTIAL LOSSES OF ANY KIND, NATURE OR DESCRIPTION WHATSOEVER (INCLUDING ECONOMIC LOSSES OR LOST PROFITS) SUFFERED OR INCURRED BY SUCH PARTY ARISING UNDER OR IN CONNECTION WITH THIS AGREEMENT OR AS A RESULT OF ANY ACTIVITIES HEREUNDER, REGARDLESS OF WHETHER ARISING FROM BREACH OF CONTRACT, WARRANTY, TORT, STRICT LIABILITY OR OTHERWISE, EVEN IF SUCH PARTY IS ADVISED OF THE POSSIBILITY OF SUCH LOSS OR DAMAGE OR IF SUCH LOSS OR DAMAGE COULD HAVE BEEN REASONABLY FORESEEN.

13.6 Insurance. Not later than thirty (30) days before the date of the First Commercial Sale of any Product, Bion will, at its expense, and CoreRx will, at its expense, obtain and maintain in full force and effect, comprehensive general liability insurance, including product liability insurance with a minimum coverage of $2,000,000 per occurrence (or claim) and $5,000,000 in the aggregate limit of liability per year. Each Party shall have included the other Party as an additional insured to such Party's insurance policy. Upon a Party's reasonable request, the other Party hereto shall provide the requesting Party with certified copies of all applicable endorsements and certificates of insurance, both evidencing such coverage, which shall also state that a minimum of thirty (30) calendar days prior written notice of any proposed cancellation, or expiration without renewal, and five (5) Business Days' prior written notice of any proposed change in carriers or material terms of coverage. If the above policies are reported on a "claims made basis" then the applicable Party shall provide coverage five (5) years after the Agreement has terminated. For clarity, the foregoing insurance requirements shall not in any way limit either Party's liability with respect to its indemnification or other obligations under this Agreement.

ARTICLE 14. TERM AND TERMINATION

14.1 Term. This Agreement shall commence on the Effective Date and shall continue in full force and effect for a period of five (5) years from the commercialization of the last Product, unless earlier terminated pursuant to this Article 14 or mutually terminated by the Parties in writing (such period of time as this Agreement is in effect, the "**Term**"). At the request of Bion during the Term, the Parties shall negotiate in good faith a renewal of this Agreement in whole or on a Product-by-Product basis; provided, however, that as part of such negotiations, either Party may propose alternative terms, including alternative financial terms, which may apply during any such renewal period. For clarity, (i) neither Party shall have any obligation to renew this Agreement unless and until agreed to by such Party, and (ii) unless otherwise expressly agreed to by the Parties in writing, any new or different terms which are negotiated as part of the renewal, if any, shall only apply during the renewal period and shall

not in any way alter the terms of this Agreement during the initial Term.

14.2 Breach. If either Party shall materially breach this Agreement (or a given Addendum to the extent that the material breach relates solely to such Addendum or the Product thereunder), the non- breaching Party may give written notice to the other Party, specifying the nature of the material breach and, if such material breach is not remedied within thirty (30) calendar days of receipt of such notice (provided, however, that the cure period shall be suspended during any time that a Party seeks resolution of a dispute as to whether an alleged material breach occurred pursuant to any dispute resolution mechanisms under this Agreement), then the non-breaching Party shall have the right, in its sole discretion, immediately to terminate this Agreement upon written notice to the breaching Party. Notwithstanding the foregoing, if such material breach relates only to a given Product, then the non- breaching Party shall only have the right to terminate the applicable Addendum to which such material breach relates and this Agreement, and all other Addenda shall not be affected by such termination.

14.3 Bankruptcy. This Agreement may be terminated by written notice given by a Party upon the occurrence of any of the following with respect the other Party: (a) such other Party becomes insolvent, or (b) voluntary or involuntary proceedings by or against such other Party are instituted in bankruptcy or under any insolvency law, which proceedings, if involuntary, shall not have been dismissed within ninety (90) days after the date of filing, or (c) a receiver or custodian is appointed for such other Party, or proceedings are instituted by or against such other Party for corporate reorganization or the dissolution of such other Party, which proceedings, if involuntary, shall not have been dismissed within ninety (90) days after the date of filing, or (d) such other Party makes an assignment of substantially all of its assets for the benefit of its creditors, or substantially all of the assets of such other Party are seized or attached and not released within ninety (90) days thereafter.

14.4 Study Failure. In the event that any required or agreed study(ies) for a Product, including, without limitation, Bio-Equivalence Studies, fail more than two (2) times, Bion may terminate this Agreement with respect to the applicable Product upon ten (10) Business Days' notice to CoreRx.

14.5 Termination for Refusal to File. In the event that FDA issues a "Refusal To File" for a Product Regulatory Approval application because of a deficiency arising out of the dossier provided by CoreRx for the preparation of such application for Regulatory Approval, Bion shall reasonably work together in good faith with CoreRx and provide CoreRx one-hundred and eighty (180) calendar days to cure such problem so that Bion may re-file an application for Regulatory Approval that addresses the reasons for the refusal to file. In the event that a second refusal to file is received, or Bion believes in good faith, after reasonable consultation with CoreRx after the aforementioned one hundred eighty (180) calendar days allowed to resolve the problems associated with the "Refusal To File", that it is commercially unreasonable to re-file, Bion may terminate this Agreement with respect to the applicable Product upon thirty (30) calendar days' notice to CoreRx.

14.6 Termination for Efficacy Study Requirement. If applicable and in the event that FDA determines that the formulation of a Product shall not be eligible for final Regulatory Approval in the absence of efficacy or clinical studies, then Bion may terminate this Agreement with respect to the applicable Product upon sixty (60) calendar days' notice to CoreRx. Such termination shall be deemed an expiration of this Agreement with respect to the applicable Product pursuant to Section 14.1 and neither Party shall be deemed to have breached this Agreement as a result of such determination by FDA or to have any liability at law or equity to the other as a result of such termination.

14.7 Termination for Supply Interruption. Bion may terminate this Agreement pursuant to a Supply Interruption pursuant to Section 5.11.

14.8 Termination for Force Majeure. Bion may terminate this Agreement in the event of a Force Majeure that lasts for more than one hundred twenty (120) days with notice to CoreRx.

14.9 Termination for Government or Legal Action. Bion may terminate this Agreement with notice to CoreRx if (i) a permanent injunction is issued by a court of competent jurisdiction enjoining Bion's

sale of a Product; or (ii) sale of a Product has been enjoined or is the subject of active litigation that claims that the Manufacture or sale of the Product infringes a Third Party Patent Rights or market exclusivity rights.

14.10 Consequences of Expiration or Termination.

14.10.1 In the event that this Agreement is terminated in accordance with Sections 14.2 or 14.7, Bion shall have the right (but not the obligation) to (a) keep any or all outstanding Firm Orders in place, in which case CoreRx shall Manufacture and Deliver, in accordance with this Agreement, all quantities of Products ordered pursuant to such Firm Orders (regardless of whether the Delivery Date for such Products is before or after such termination) and Bion shall pay the Transfer Price with respect to such Products which meet the representations, warranties and covenants set forth in this Agreement or (b) cancel any or all outstanding Firm Orders, and with respect to any such cancelled Firm Orders, Bion shall have no further liability with respect thereto; provided that Bion shall only have the right to cancel Firm Orders pursuant to this clause (b) if this Agreement is terminated by Bion pursuant to Section 14.2 or Section 14.7.

14.10.2 Reserved.

14.10.3 Upon the expiration or termination of this Agreement, CoreRx shall assist Bion in effecting a smooth transition to an alternate supplier(s) for the manufacture of Products. Without limiting the generality of the foregoing, at the request of Bion, CoreRx shall support the technical transfer of the Manufacture of the Product to an alternate source(s) (including as set forth in Section 2.10).

14.10.4 Upon expiration or termination of this Agreement (or a given Addendum, as applicable), Bion and CoreRx shall immediately settle all outstanding invoices and other monies owed to the other pursuant to this Agreement (or such Addendum, as applicable). The termination or expiration of this Agreement (or a given Addendum, as applicable) shall not affect the rights and obligations of the Parties accruing prior to such termination or expiration. Subject to the foregoing, expiration or termination of this Agreement (or a given Addendum, as applicable) shall relieve and release all Parties from any liabilities and obligations under this Agreement (or such Addendum, as applicable), other than those specifically set forth in this Section 14.10 and those that survive termination in accordance with Section 14.12.

14.10.5 If this Agreement is terminated by Bion in accordance with Section 14.3 or Section 14.7, then the Parties agree to implement a transition plan, and to negotiate in good faith to allow Bion to lease the equipment, space, and personnel used to manufacture the Products pursuant to this Agreement, or acquire the Facility, equipment, and personnel used to manufacture the Products pursuant to this Agreement from CoreRx, provided such lease or acquisition will be structured in a manner that does not adversely impact another CoreRx customer then using another portion of the Facility for the production of products at the time of termination.

14.10.6 In the event that this Agreement is terminated in its entirety, then all Addenda then in effect shall automatically terminate as of the date of termination of this Agreement.

14.11 Termination of Individual Addendum. In the event that only a given Addendum expires or is terminated, as applicable, then the foregoing provisions of this Article 14 shall only apply to such Addendum and the Product thereunder.

14.12 Survival. In the event of a termination or expiration of this Agreement, only the following provisions shall survive termination or expiration: Articles 1, 10 (to the extent applicable), 11, and 13, and Sections 6.5-6.7, 7.5-7.6, 7.9, 8.1-8.2, 8.8, 12.8, 16.1-16.6, 16.8 and 16.10-16.12.

ARTICLE 15. COMPANY EVENTS

15.1 CoreRx Company Event. If CoreRx determines to commence the process for the sale of CoreRx, then CoreRx shall, within seven (7) days of the Board of Director's determination to commence such sale process, provide a written notice to Bion, setting forth the intent of CoreRx to

commence a sale process and written assurances that CoreRx will continue to comply with the terms of this Agreement.

15.2 Assignment. This Agreement shall be binding upon and inure to the benefit of each of the Parties hereto and their respective successors and approved assigns, provided, however, that CoreRx may not assign or transfer this Agreement whether by operation of law or otherwise without the prior written consent of Bion (which shall not be unreasonably withheld, conditioned or delayed). Each Party may assign this Agreement or grant a security interest in this Agreement as collateral security for purposes of obtaining financing or to any Party's lenders as collateral security. Subject to compliance with Section 15.1, no consent shall be required for a Party to assign this Agreement or transfer this Agreement by operation of law is in connection with a merger or acquisition or sale of all or substantially all of the assets of the assigning Party or to assign this Agreement to an Affiliate (provided, however, in the case of CoreRx, such Affiliate must be able to discharge its obligations under this Agreement including the various Addendums and CoreRx shall continue to remain responsible for the acts or omissions of such Affiliate). This Agreement shall be binding upon and shall inure to the benefit of the Parties and their successors and permitted assigns. Any assignment or transfer in contravention of this Agreement shall be null and void.

ARTICLE 16. MISCELLANEOUS

16.1 Interpretation and Construction. Unless the context of this Agreement otherwise requires, (i) the terms "include," "includes," or "including" shall be deemed to be followed by the words "without limitation" unless otherwise indicated; (ii) words using the singular or plural number also include the other; (ii) the terms "hereof," "herein," "hereby," and derivative or similar words refer to this entire Agreement; (iv) the terms "Article," "Section" and "Attachment" refer to the specified Article, Section and Attachment of this Agreement, and (v) words of any gender include each other gender. Whenever this Agreement refers to a number of days, unless otherwise specified, such number shall refer to calendar days. The headings and paragraph captions in this Agreement are for reference and convenience purposes only and shall not affect the meaning or interpretation of this Agreement. This Agreement shall not be interpreted or constructed in favor of or against either Party because of its effort in preparing it.

16.2 Independent Contractor Status. The Parties shall at all times act as and be deemed to be independent contractors. Nothing in this Agreement shall be construed to render either Party as the agent, partner, joint venturer or employee of the other Party for any purpose whatsoever, and neither Party shall have any authority to enter into any contracts (other than settlement agreements pursuant to the applicable provisions of this Agreement) or assume any obligations for the other Party nor make any warranties or representations on behalf of that other Party.

16.3 Waiver. The waiver by either Party of a breach of any provision contained herein shall only be effective if in writing and shall in no way be construed as a waiver of any succeeding breach of such provision or obligation or the waiver of the provision or obligation itself.

16.4 Severability. If any provision of this Agreement shall be held illegal or unenforceable, that provision shall be limited or eliminated to the minimum extent necessary so that this Agreement shall otherwise remain in full force and effect and enforceable.

16.5 Further Assurances. Each Party hereto agrees to execute, acknowledge and deliver such further instruments and documents, and to do all such other acts, as may be reasonably necessary or appropriate in order to carry out the purposes and intent of this Agreement

16.6 Notices. Any notice or other communication to be given under this Agreement by any Party to any other Party shall be in writing and shall be either (a) personally delivered, (b) mailed by registered or certified mail, postage prepaid with return receipt requested, (c) delivered by reputable overnight express delivery service or same-day local courier service, (d) delivered by confirmed (or answered back) telex or facsimile transmission, to the address of the applicable Party as set forth below, or to

such other address as may be designated by the Parties from time to time in accordance with this Section 16.6. Notices delivered personally, by overnight express delivery service or by local courier service shall be deemed given as of actual receipt. Mailed notices shall be deemed given ten (10) Business Days after mailing and five (5) Business Days after expedited mailing services. Notices delivered by telex or facsimile transmission shall be deemed given upon receipt by the sender of the answerback (in the case of a telex) or transmission confirmation (in the case of a facsimile transmission); provided, however, that telex or facsimile that is sent after 5:00 pm (recipient's local time) shall be deemed given at 9:00 am (recipient's local time) on the next Business Day.

If to Bion at:
Bionpharma Inc.
600 Alexander Road, Suite 2-4B
Princeton, NJ 08540
Telecopier: (609) 380-3311
With a copy by email to admin@bionpharma.com

If to CoreRx at:
CoreRx Inc.
14205 Myerlake Circle
Clearwater, FL 33760
Telecopier: (727) 259-6971

With a copy by email to todd.daviau@corerxpharma.com.

or to such other address as each Party may designate for itself by like written notice.

16.7 Dispute Resolution. The Parties shall initially attempt in good faith to resolve any significant controversy, claim, allegation of breach or dispute arising out of or relating to this Agreement (hereinafter collectively referred to as a "**Dispute**") through negotiations between senior executives of Bion and CoreRx. If the Dispute is not resolved within thirty (30) calendar days (or such other period of time mutually agreed upon by the Parties) of notice of the Dispute, then the Parties agree to submit the Dispute to non-binding mediation in an attempt to resolve the Dispute. Unless otherwise mutually agreed by the Parties, only if the Dispute is not resolved through negotiations or non-binding mediation as set forth herein, may a Party resort to litigation.

16.8 Governing Law, Jurisdiction and Waiver of Jury Trial. This Agreement shall be governed by and construed in accordance with the laws of the State of New York. The United Nations Convention on International Sales of Goods shall not apply to the transactions contemplated by this Agreement. The Parties irrevocably agree that the State and Federal Courts located in the State, City, and County of Southern District of New York, shall have exclusive jurisdiction to deal with any disputes arising out of or in connection with this Agreement and that venue is proper in such Courts, and each Party irrevocably and unconditionally consents to submit to the exclusive jurisdiction of the courts of the Southern District of New York and agrees not to bring any claim regarding such a dispute in any other court, and to waive unconditionally any objection to the laying of venue in such forum, including any claim of inconvenient forum. Each Party hereby expressly consents and submits to the personal jurisdiction of the Federal and State Courts in the State and County of the Southern District of New York. EACH PARTY HERETO WAIVES, TO THE FULLEST EXTENT PERMITTED BY APPLICABLE LAW, ANY RIGHT IT MAY HAVE TO A TRIAL BY JURY IN RESPECT OF ANY SUIT, ACTION OR OTHER PROCEEDING ARISING OUT OF THIS AGREEMENT.

16.9 Force Majeure. A Party shall not be liable for nonperformance or delay in performance, except for defaulted obligations of payment, to the extent that such nonperformance or delay in performance is not due to its negligence and is caused by any event reasonably beyond the control of such Party, including wars, hostilities, revolutions, riots, civil commotion, national emergency, strikes, lockouts, unavailability of supplies, epidemics, fire, flood, earthquake, force of nature, explosion, terrorist act,

embargo, or any other Act of God, (each a **"Force Majeure Event"**). In the event of any such delay, the delayed Party may defer its performance for a period equal to the time of such delay, provided that the delayed Party gives the other Party written notice thereof promptly and, in any event, within thirty (30) calendar days of discovery thereof, and uses its good faith efforts to cure the excused breach. In the event of a Force Majeure that lasts for more than one hundred twenty (120) days, then Bion shall have the right upon written notice to CoreRx to terminate this Agreement or any one or more Addenda in accordance with Section 14.8.

16.10 Entire Agreement; Amendments. This Agreement and any Attachments and Schedules attached hereto, constitute the entire agreement between CoreRx and Bion with respect to the Products in the Territory and supersede all prior representations, understandings and agreements with respect to such Products, including the Confidentiality Agreement effective October 16, 2014 between the Parties. Furthermore, this Agreement shall supersede any and all pre-printed terms on any orders, invoices, and other related documents and any and all orders issued by CoreRx. This Agreement may only be amended by a statement in writing to that effect signed by duly authorized representatives of Bion and CoreRx. The intent of this Agreement is to include items necessary for the proper execution and completion of the performance under this Agreement. The documents comprised by this Agreement are complementary, and what is required by any one shall be as binding as if required by all. Words and abbreviations that have known or technical trade meanings are used in this Agreement in accordance with such recognized meanings. In the event of a conflict or inconsistency between this Agreement and any exhibit, schedule and attachments, the terms and conditions of this Agreement shall prevail.

16.11 Counterparts. This Agreement may be executed in one or more counterparts, including by transmission of facsimile or PDF copies of signature pages, each of which shall for all purposes are deemed to be an original and all of which together shall constitute one instrument.

16.12 Third Party Beneficiaries. No term or provision of this Agreement is intended to be, or shall be, for the benefit of a sub-contractor, supplier, any individual member of the control group utilized for the bioequivalence studies, firm, organization, or corporation not a party hereto, and no such other Person, firm, organization or corporation shall have any right or cause of action hereunder.

16.13 Use of Affiliates. Bion shall have the right to exercise its rights and perform its obligations under this Agreement either itself or through any of its Affiliates, provided that Bion shall remain solely responsible for the acts, omissions and performance of such Affiliate as if such acts, omissions and performance had been provided by Bion itself under this Agreement. In addition, in each case where a Party's Affiliate has an obligation pursuant to this Agreement or performs an obligation pursuant to this Agreement (to the extent permitted hereunder), (i) such Party shall cause and compel such Affiliate to perform such obligation and comply with the terms of this Agreement and (ii) any breach of the terms or conditions of this Agreement by such Affiliate shall be deemed a breach by such Party of such terms or conditions.

[Remainder of this page intentionally left blank signature page follows]

IN WITNESS WHEREOF, the Parties have caused this Agreement to be duly authorized, executed, and delivered this Agreement intending it to take effect as of the Effective Date.

CORERX INC.

Name:
Title: President and Chief Executive Officer

IN WITNESS WHEREOF, the Parties have caused this Agreement to be duly authorized, executed, and delivered this Agreement in tending it to take effect as of the Effective Date.

BIONPHARMA INC.

11/24/2020

Name: Venkat Krishnan
Title: President and Chief Executive Officer

IN WITNESS WHEREOF, the Parties have caused this Agreement to be duly authorized, executed, and delivered this Agreement in tending it to take effect as of the Effective Date.

BIONPHARMA INC.

Name: Venkat Krishnan
Title: President and Chief Executive Officer

ATTACHMENT 1
PRODUCTS

Table 1. Identification of Reference Product

Product	API	Dosage Form; Route	Strengths	Proprietary Name
Enalapril Solution	Enalapril Powder for Oral Solution	Solution	1mg/mL	Epaned®

ATTACHMENT 2 has been intentionally omitted.

Exhibit 1 to Addendum Product Specifications

(See Attached)

[Attach Specifications as Exhibit 1]

Exhibit 2 to Addendum Certain Bion Intellectual Property

(See Attached)

[List relevant Bion Intellectual Property on this Exhibit 2]